

# ACTA PÆDIATRICA

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REDIGENDA CURAVIT  
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VOL. XXXIX

MCML

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1950





JUN 14 1950

V. 39 2 suppl 78-79

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A. LICHTENSTEIN  
KRONPRINSESSAN LOVISAS BARNSJUKHUS,  
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Vol. XXXIX. Fasc. 1-2

1950

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# ACTA PÆDIATRICA

PROFESSOR A. LICHTENSTEIN

KRONPRINSESSAN LOVISAS BARNSJUKHUS,

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FROM KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROF. A. LICHTENSTEIN, M. D. CONSULTANT CARDIOLOGIST:  
E. MANNHEIMER, M. D.

## **Mechanically Induced Disturbances in the Heart Action**

### **Observations Made on Heart Catheterization of One Hundred and Forty-Two Children**

By

**BERNHARD LANDTMAN**

The introduction of heart catheterization as a clinical method has considerably increased the possibilities of studying the physiology and pathology of the cardiac function. This method is of particular value in ascertaining the possibilities of surgical correction of congenital heart disease. At Kronprinsessan Lovisa's Children's Hospital about one hundred and sixty heart catheterizations have been performed up to the present time mainly with this object in view. No complications of clinical importance have so far been observed in this material. Some few patients have shown signs of slight collapse during catheterization but these signs have disappeared spontaneously after the examination was finished.

When this method of investigation was started at this hospital about two years ago it was observed that irregularities in the heart action frequently occurred during catheterization. A more systematic study of this problem showed that these disturbances are produced in almost every case. As a rule, however, these are transient phenomena; for instance one ectopic beat may be the only irregularity during the whole examination. Therefore careful electrocardiographic recording of the heart action during the various phases of the catheterization is necessary to detect the majority of these disturbances. It is, perhaps, due to this fact that there are no extensive studies of this problem published in

the literature although many authors have described arrhythmias arising during heart catheterization (BATTRO and BIDOGLIA 1947, HECHT 1947, DEXTER et al. 1947, JOHNSON et al. 1947, DUCHOSAL et al. 1948, BING et al. 1949, COBLENTZ et al. 1949, LEVINE et al. 1949, MANNHEIMER et al. 1949, and others).

In accordance with the research program in this department the object of the present study was by means of electrocardiography, phonocardiography and recording of the intracardiac pressure, to get a further insight into these mechanically produced disturbances in the heart action.

#### Method and Material

The technique of heart catheterization such as performed at Kronprinsessan Lovisa's Children's Hospital was described in detail by LAGERLÖF, MANNHEIMER, and WERKÖ (1949). In this connection some main points only will be stressed. The catheters used were the usual ureteric catheters, mostly nr. 7, as modified by Cournand. In none of the cases included in this material was any general anaesthesia used. The catheter was inserted under local anaesthesia as a rule through a median basilic vein of the left arm as far as the upper axilla. From this point, under fluoroscopic guidance, the tip of the catheter was manipulated into the superior vena cava, the right auricle through the tricuspid valve into the right ventricle and thence through the infundibulum into the pulmonary artery, usually ending in its right branch (Fig. 1).

The exact position of the tip of the catheter during the examination was checked not only by fluoroscopy but also by recording of the intracardiac pressure. Further evidence could be obtained from the oxygen content of the blood. As a rule the tip of the catheter was first introduced into the pulmonary artery, where blood samples were taken and the electrocardiogram was registered. Subsequently, the electrocardiogram was followed during the entire examination, both on withdrawal of the catheter and during the intervals when the tip of the catheter was lying in the different parts of the heart where blood samples were taken.

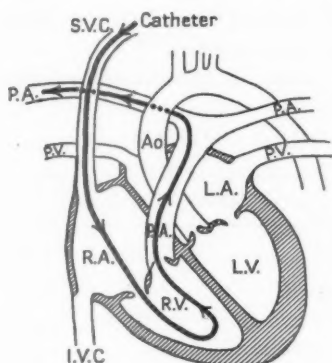


Fig. 1. The usual course of the catheter in right heart catheterization.

S.V.C. = Superior vena cava. R.A. = Right auricle. R.V. = Right ventricle. P.A. = Pulmonary artery. L.V. = Left ventricle. L.A. = Left auricle. P.V. = Pulmonary vein. Ao = Aorta. I.V.C. = Inferior vena cava.

In some instances electrocardiograms were also taken when the catheter was introduced into the heart, but this method was abandoned since the disturbances in the heart action which could be observed corresponded to those which were registered on withdrawal of the catheter.

In the majority of the cases a Swedish six channel electrocardiograph, the so-called hospital model (ELMQVIST), was used. As a rule lead I of the electrocardiogram was registered simultaneously with the phonocardiogram and the intracardiac pressure curve. In some instances the three standard leads, occasionally supplemented by two unipolar chest leads (according to WILSON), were registered simultaneously with the pressure. The phonocardiograph used was the MANNHEIMER-STORDAL model. By means of this apparatus the sound phenomena of the heart are divided into four frequency ranges, namely, below 100, 50 to 175, 175 to 400, and 400 to 1 000 cycles per second, respectively. For recording of the intracardiac pressure the capacitive manometer designed by TYBJÆRG-HANSEN and WARBURG was used. Tests have shown a lag of less than 0.01 second between the pressure tracing through the catheter and the electrical events in the heart

cycle. Before and after each tracing the zero pressure and a known standard pressure was recorded.

The material consist of 142 persons (Table 1).

Table I.

Heart catheterizations performed on 142 persons at Kronprinsessan Lovisa's Children's Hospital.

Principal diagnosis	No. of cases	Sex		Age in years				Nr. of subjects showing cardiac disturbances during catheterization
		Boys	Girls	2-5	6-10	11-15	16-20	
Normal cases .....	9	6	3	2	7			5
Atrial septal defect .....	6	2	4		3	3		3
Ventricular septal defect .....	23	12	11	6	11	6		18
Patent ductus arteriosus .....	22	9	13	6	12	4		12
Isolated pulmonary stenosis ....	18	10	8		11	6	1	9
Coarctation of the aorta .....	5	4	1	1	2	2		4
Subaortic stenosis .....								
Tetralogy of Fallot .....	45	25	20	11	23	9	2	30
Eisenmenger complex .....	10	7	3	2	8			4
Primary pulmonary hypertension	2		2			2		1
Acquired mitral disease .....	2	1	1		1	1		2
Total:	142	76	66	28	78	33	3	88

The vast majority of the patients were children below ten years of age, the youngest being two years old. There were 76 boys and 66 girls. Six children were considered normal. In these cases the only sign was a faint systolic murmur, the frequency of which was within the physiological range of variation. With some few exceptions the rest of the patients had a congenital heart disease. About one half of the patients belonged to the cyanotic group. In many instances the nature of the anomaly was confirmed by catheterization but further evidence was obtained by angiocardiography. Some of the patients had multiple abnormalities of the heart including vascular anomalies. The table only shows the principal defects.



### Results

Spontaneous disturbances in the heart action were not observed in any of the patients before or after catheterization. Apart from pathological electrocardiographic patterns typical for the different groups, e. g. left or right hypertrophy, only 6 patients showed delayed atrioventricular or intraventricular conduction time before and after catheterization. During catheterization disturbances in the heart action were registered in 88 patients (Table 1). Table 1 shows that there was no association between the occurrence of these disturbances and the nature of the heart disease. Nor could any accumulation of disturbances be observed in any special age group.

The number of various disturbances in the heart action observed during heart catheterization are listed in the right column of table 2. The total number of disturbances was 160, indicating that different kind of disturbances often occurred in the same patient during the examination. It is worth mentioning that there was no association between the various disturbances produced and the nature of the heart disease. Among the arrhythmias solitary or multiple extrasystoles of different origin were the most common (Fig. 4, 5, 6, 8, 9, 13, and 14). According to a general conception (KAHN 1909, LEWIS 1925, BARKER et al. 1930, HOLTZMANN 1945, GROEDEL and BORCHARDT 1948, and others) a ventricular ectopic contraction was regarded as originating from the right side of the heart if the chief initial deflexion was upward in lead I (Fig. 5). Ectopic contractions of left ventricular origin were considered to be those in which the chief initial deflexion was downward in lead I (Fig. 6). In a special group are 15 instances of ectopic contractions which, unlike the extrasystoles, did not occur prematurely. The interval between these ectopic beats and the preceding and succeeding nomotopic beats corresponded to the normal heart cycle (Fig. 7). Ventricular tachycardias (flutter) was observed in 22 instances (Fig. 8 and 14). Supraventricular and nodal rhythms could be registered as transient phenomena during catheterization in 4 and 6 instances, respectively (Fig. 2 and 12). Two cases of auricular flutter and an equal number of supraven-

Table 2.

One hundred and sixty disturbances in the heart action registered during heart catheterization in 88 children. Distribution of the material according to the position of the tip of the catheter when the disturbance was observed.

Disturbance in the heart action	Position of the tip of the catheter										No. of disturbances
	Pulmonary artery		Right ventricle			Right auricle	Left auricle	Pulmonary vein	Left ventricle	Aorta	
	Stem	Infundibulum	Infundibulum	Cavity	Tricuspid tract						
Extrasystoles:											
Supraventricular .....	2	1	9	4	3	1	1	1			22
Nodal .....			1	1	2	1		1	1		7
Ventricular											
Right .....	1	4	17	13	9			1	1		46
Left .....	1	2	10	3	1						17
Ectopic beats (not premature):											
Supraventricular .....		1	1	3	2	1				1	9
Ventricular											
Right .....			3	2					1		6
Ventricular tachycardia:											
Right .....			3	3	4						10
Left .....		2	5	1	2				1	1	12
Supraventricular rhythm .....	2					2					4
Nodal rhythm .....	2		1			3					6
Auricular flutter .....	1		1								2
Supraventricular tachycardia .....						1				1	2
Sino-auricular block .....				1		1					2
Incomplete atrio-ventricular block ..	1		1						1		3
Complete atrio-ventricular block ...			1	1							2
Intraventricular block .....				1			1				2
Escaped beats:											
Supraventricular .....			1	1					1		3
Nodal .....			1	1		1					3
Ventricular .....				1						1	2
No. of disturbances	10	10	55	36	23	11	2	3	6	4	160

tricular paroxysmal tachycardia were observed (Fig. 3 and 15). There were also a few cases representing various degrees and locations of disturbances in the stimulus conduction (Fig. 9, 10, and 16). Finally, 8 cases of escaped beats could be registered. In these cases the interval between the ectopic and the preceding nomotopic beat was considerably longer than the normal heart cycle (Fig. 11).

#### **Distribution of the Disturbances in the Heart Action According to the Position of the Tip of the Catheter**

The vast majority of disturbances in the heart action were registered when the tip of the catheter was touching certain limited regions of the heart. Regions in which arrhythmias could easily be produced were the infundibulum between the right ventricle and the pulmonary artery, the tricuspid area and the rest of the right ventricular cavity. More seldom disturbances were registered when the tip of the catheter was situated in the stem and branches of the pulmonary artery or in the right auricle. No disturbances in the heart action were noticed when the tip of the catheter was passing the superior vena cava. These observations seem to indicate that the disturbances in the heart action were produced mainly by mechanical stimulation of the slightly curved catheter tip on the subendocardial specific muscular system, since the stimulation produced by the rest of the catheter remained practically the same during the withdrawal of the catheter from the heart.

In table 2 the various disturbances in the heart action are divided into 10 groups according to the position of the catheter tip when the disturbance was first registered. In view of the fact that there was no correlation between the type of disturbance and the age and sex of the patient or the nature of the heart disease these three factors are not considered in the table.

Disturbances in the heart action registered when the tip of the catheter was in the pulmonary artery. In 78 of these patients (86 per cent) it was possible to introduce the tip of the catheter into the pulmonary artery. Twenty various

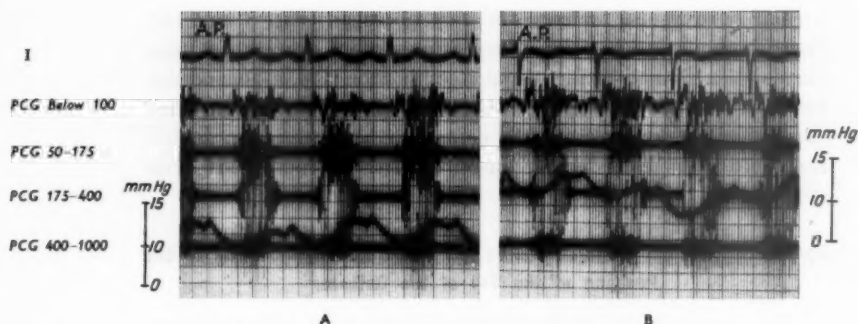


Fig. 2. Girl, aged 4 years. Diagnosis: Ventricular septal defect.

A. Tracing recorded when the tip of the catheter was placed in the right branch of the pulmonary artery. Normal sinus rhythm. Loud systolic murmur up to 1000 cycles per second. Pressure about 13/10 mm Hg.

B. Ectopic supraventricular rhythm registered as a transient phenomenon when the tip of the catheter was withdrawn towards the right ventricle. The systolic murmur and the pressure in the pulmonary artery have not changed.

disturbances in the heart action occurred in this group (26 per cent). In 10 of these cases irregularities were registered when the tip of the catheter was situated in the main stem of the pulmonary artery or its right branch. An equal number of disturbances were produced by the catheter tip in the infundibulum of the pulmonary artery.

Extrasystoles of different origin were the commonest arrhythmia observed (11 instances in the whole group). One case of ectopic beats without alteration in the dominant rhythm was registered when the tip of the catheter was passing through the infundibular region of the pulmonary artery. Fig. 7 shows similar ectopic beats induced by the catheter tip in the right ventricular cavity. Tachycardia of left ventricular origin was registered in 2 cases when the catheter tip was touching the infundibular region of the pulmonary artery. In 2 instances a normal sinus rhythm was suddenly changed into a supraventricular rhythm when the catheter was slowly withdrawn from the periphery of the pulmonary artery towards the right ventricle. These ectopic rhythms lasted for about 20 to 30 beats. When the tip of the catheter reached the right ventricle the rhythm was again

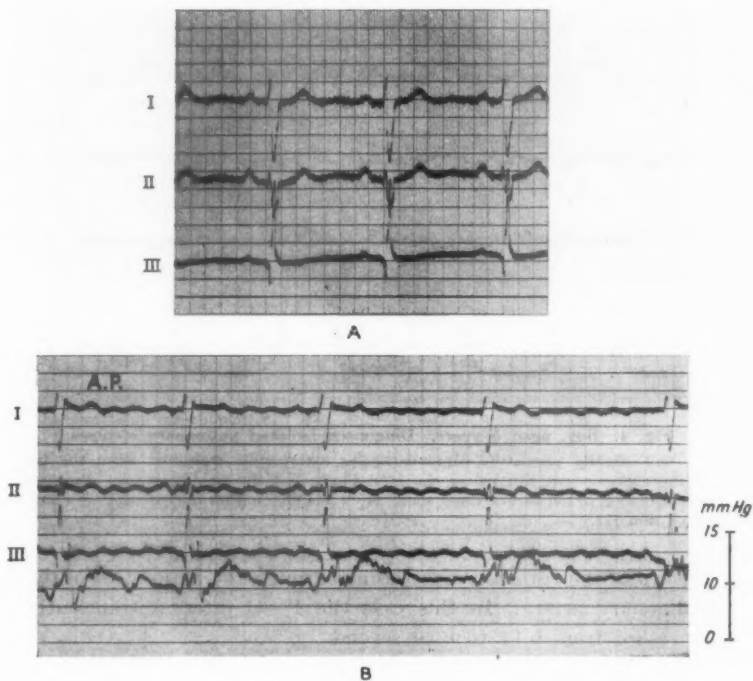


Fig. 3. Boy, aged 16 years. Diagnosis: Tetralogy of Fallot.

A. Standard electrocardiogram before and after catheterization.

B. Auricular flutter with a 5:1 to 7:1 block registered when the tip of the catheter was inserted into the right branch of the pulmonary artery. Pressure about 10 mm Hg. The arrhythmia lasted throughout the catheterization.

replaced by the original sinus rhythm, which remained unaltered throughout the examination (Fig. 2). There were 2 similar cases in which a nodal rhythm was registered as a transient phenomenon when the catheter tip was passing through the main stem of the pulmonary artery. In one case auricular flutter was induced when the catheter tip was inserted into the right branch of the pulmonary artery. This arrhythmia lasted throughout the examination until the catheter was withdrawn from the heart (Fig. 3). In one case an incomplete atrio-ventricular block appeared when

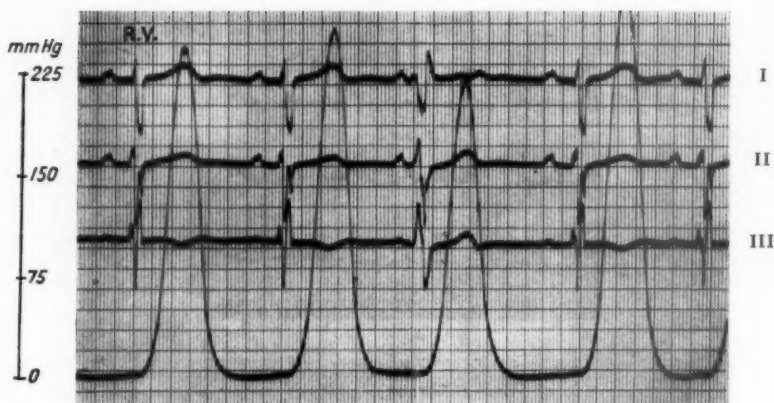


Fig. 4. Boy, aged 5 years. Diagnosis: Isolated pulmonary stenosis.

One slightly premature supraventricular extrasystole registered when the tip of the catheter was situated in the infundibulum of the right ventricle. Pressure corresponding to the normal beats about 240/0 mm Hg, and for the extrasystole about 225/0 mm Hg.

the tip of the catheter was passing through the main stem of the pulmonary artery. In this case the P—Q interval transiently increased from 0.14 to 0.20 second.

Disturbances in the heart action registered when the tip of the catheter was in the right ventricle. The tip of the catheter could be inserted into the different parts of the right ventricle in 87 of these patients (99 per cent). Table 2 shows that 55 of the irregularities (63 per cent) were registered when the tip of the catheter was situated in the infundibular region of the right ventricle. The corresponding figures when the tip was in the right ventricular cavity and in the tricuspid area were 36 and 23, respectively (41 and 26 per cent, respectively). The distribution of the different disturbances in these three groups can be seen from the table. Solitary and multiple extrasystoles of different origin formed the commonest arrhythmia observed (Fig. 4, 5, and 6). It might be stressed that the ventricular extrasystoles which were registered when the tip of the catheter was

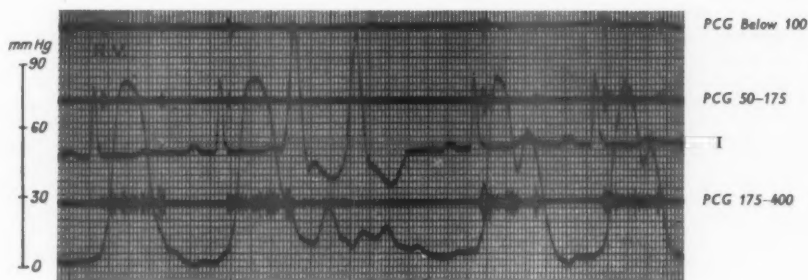


Fig. 5. Boy, aged 11 years. Diagnosis: Tetralogy of Fallot.

Two extrasystoles of right ventricular origin registered when the tip of the catheter was stimulating the wall of the right ventricular cavity. Loud systolic murmur up to 400 cycles per second. Pressure corresponding to the normal beats of about 80/0 mm Hg. Notice the low pressure and the diminishing of the murmur corresponding to the premature contractions.

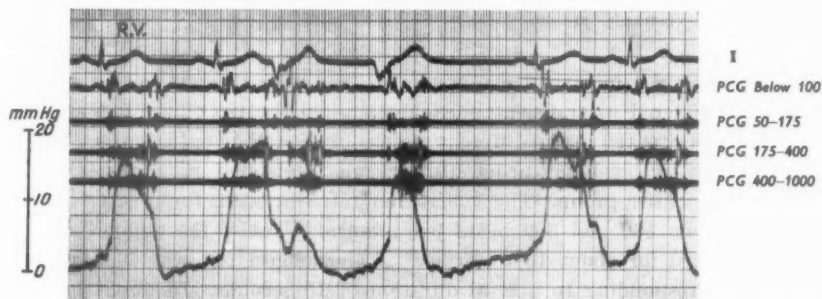


Fig. 6. Boy, aged 8 years. Diagnosis: Ventricular septal defect.

Two extrasystoles of left ventricular origin registered when the tip of the catheter was situated in the infundibulum of the right ventricle. Loud systolic murmur up to 1000 cycles per second. Pressure of about 15—20/0 mm Hg corresponding to the normal beats. Notice the marked fall of the pressure particularly during the first ectopic contraction and the shortening of the systolic murmur.

touching the infundibulum originated from the right ventricle in 17 and from the left ventricle in 10 cases. In the right ventricular cavity and in the tricuspid area, on the other hand, the left ventricular type could not be produced so often by the catheter. Eleven cases of single or multiple ectopic contractions in which

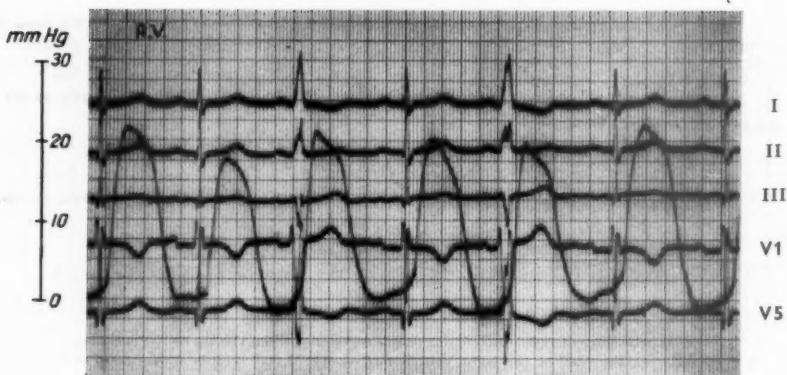


Fig. 7. Boy, aged 3 years. Diagnosis: Patent ductus arteriosus.

Two ectopic contractions of supraventricular origin occurring when the tip of the catheter was withdrawn through the tricuspid area of the right ventricle. Notice the normal interval between the ectopic beats and the normal beats and the unaltered right ventricular pressure.

the pulse interval corresponded to the normal heart cycle were registered as transient phenomena when the tip of the catheter was situated in the different regions of the right ventricle (Fig. 7). Ventricular tachycardia (flutter) was registered in 18 cases in the entire group. The ventricular rate varied in these cases between 160 and 300 beats per minute. Usually the tachycardia lasted for about 10 to 30 beats. The longest run was 60 beats, corresponding to a total duration of 15 seconds. In about half of the number of the cases the tachycardia was of left ventricular origin. Fig. 8 shows right and left ventricular tachycardia and ectopic beats of different origin registered when the tip of the catheter was slowly withdrawn from the infundibulum towards the tricuspid area. Supraventricular rhythms and auricular flutter could be registered as transient phenomena in solitary cases when the tip of the catheter was touching the infundibulum or the endocardium of the right ventricular cavity.

Among disturbances in the stimulus conduction one case of sino-auricular block with dropped ventricular beats was observed when the tip of the catheter was situated in the right ventricular



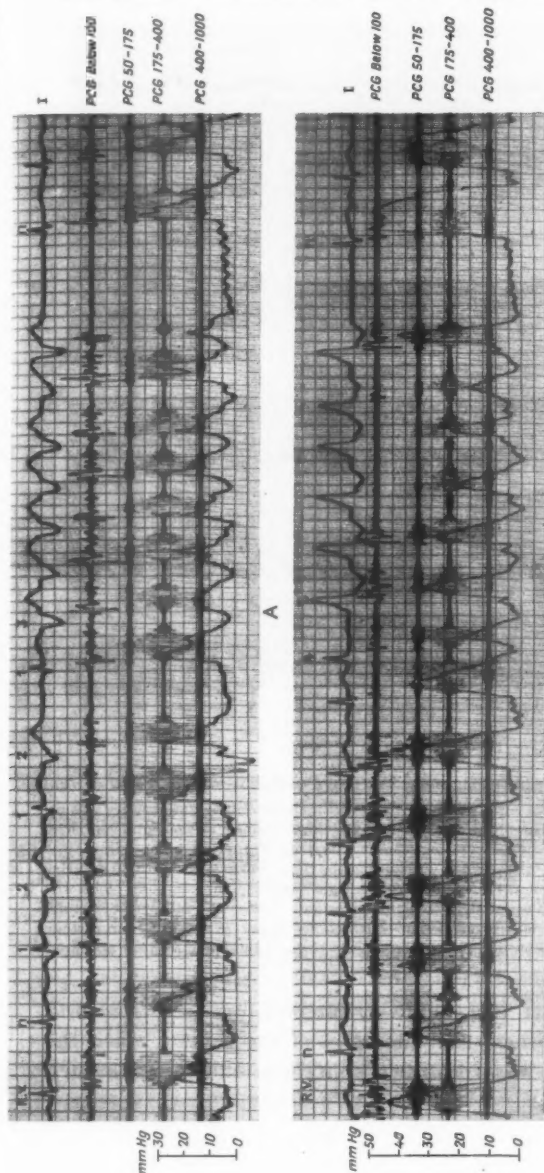


Fig. 8. Girl, aged 6 years. Diagnosis: Ventricular septal defect.

Loud systolic murmur up to 1000 cycles per second. Right ventricular pressure about 45/0 mm Hg. Tracings recorded when the tip of the catheter was slowly withdrawn from the infundibulum through the right ventricle into the tricuspid area.

A. In the infundibulum of the right ventricle the normal rhythm (n) was interrupted by solitary supraventricular (1) and left ventricular ectopic beats (2). Subsequently a tachycardia of left ventricular origin lasting for 7 beats occurred (3). On withdrawal of the catheter through the right ventricular cavity some solitary extrasystoles of the same left ventricular origin were registered (not visible on the film).

B. The tracing shows in the beginning 6 normal beats (n). When the tip of the catheter reached the tricuspid tract one nodal extrasystole (4) was registered. Immediately after this ectopic beat a tachycardia of right ventricular origin started (5). This flutter lasted for 6 beats. When the right auricle was reached by the catheter tip no disturbances in the heart action were registered anymore. Notice in both of the tracings the fall in the intra-ventricular pressure and the diminishing and shortening of the systolic murmur during the premature ectopic contractions.

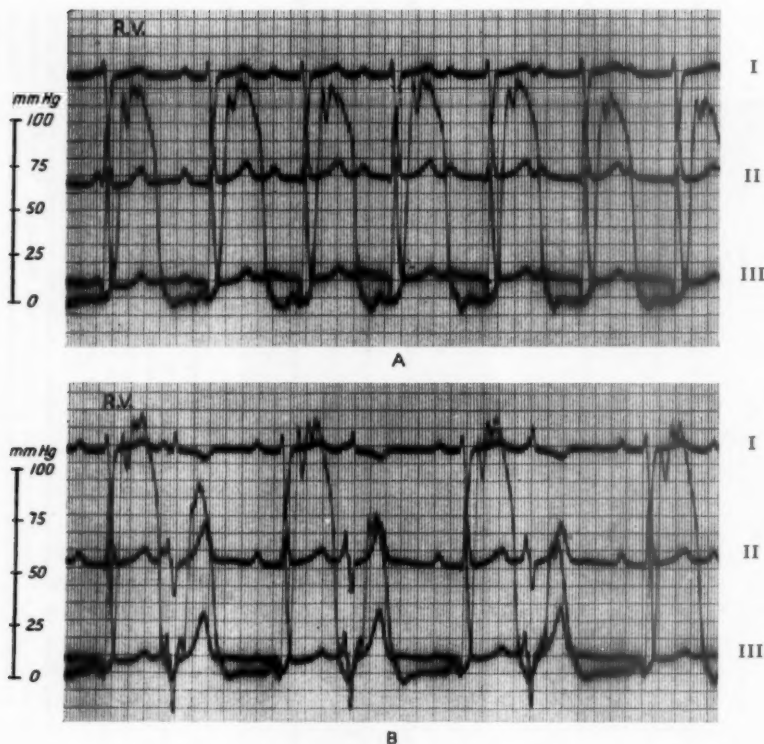


Fig. 9. Girl, aged 7 years. Diagnosis: Tetralogy of Fallot + atrial septal defect.

A. A complete dissociation between the auricular and ventricular activity arising when the tip of the catheter was inserted into the infundibulum of the right ventricle. No dropped ventricular beats were registered. The original rhythm was of sinus type with a P—Q interval of 0.16 second. Pressure in the right ventricle about 125/0 mm Hg.

B. On withdrawal of the catheter into the right ventricle the complete block was complicated by a bigeminy of right ventricular origin. Notice the fall of the systolic pressure during the premature ventricular contractions (about 75 mm Hg). On further withdrawal of the catheter into the right auricle the original sinus rhythm appeared again.

cavity. In another case the P—Q interval increased from 0.12 to 0.18 second without any alteration of the rhythm when the tip of the catheter was withdrawn from the infundibulum through the right ventricle.

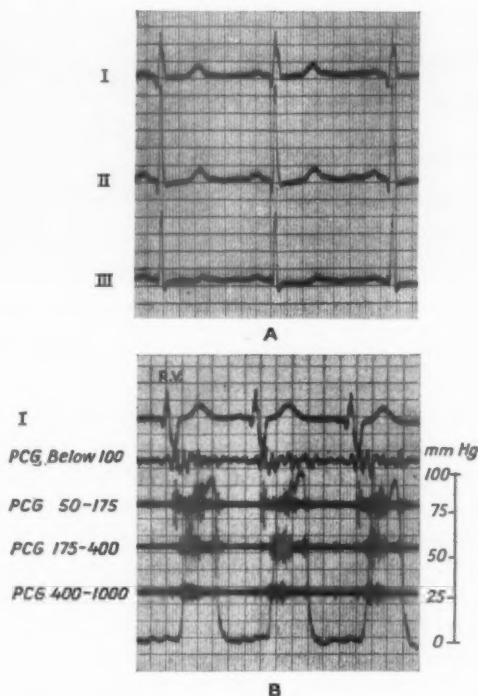


Fig. 10. Boy, aged 7 years. Diagnosis: Patent ductus arteriosus + ventricular septal defect.

A. Standard electrocardiogram before and after catheterization.

B. Right bundle branch block appearing when the tip of the catheter was withdrawn from the infundibulum of the right ventricle. P—Q interval unaltered. Loud systolic murmur over the apex up to 1000 cycles per second. Pressure in the right ventricle about 90/0 mm Hg. The block lasted throughout catheterization. Seven days later catheterization was performed again under the same conditions but no block appeared.

Fig. 9 shows a complete dissociation between the auricular and the ventricular activity. This disturbance was registered when the tip of the catheter was inserted into the infundibulum of the right ventricle. When the catheter was withdrawn through the right ventricular cavity the complete heart block was complicated by a ventricular bigeminy. On further withdrawal of

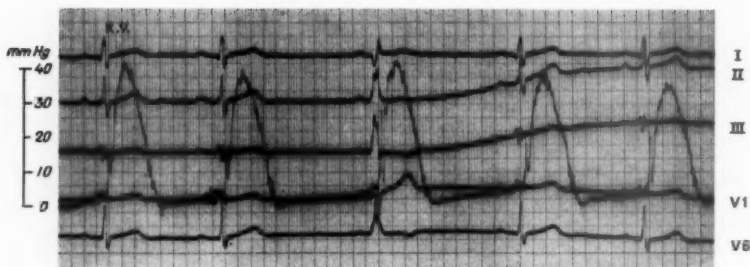


Fig. 11. Girl, aged 14 years. Diagnosis: Isolated pulmonary stenosis.

One escaped beat of supraventricular origin registered when the tip of the catheter touched the wall of the right ventricular cavity. Notice the unaltered pressure of about 40/0 mm Hg.

the catheter the rhythm again became normal when the catheter tip reached the right auricle.

There was one case of delayed intraventricular conduction which appeared when the catheter was withdrawn from the pulmonary orifice into the right ventricle (Fig. 10). This disturbance lasted throughout the whole examination. Seven days later the catheterization was performed again under the same conditions but apart from some extrasystoles no other disturbances in the heart action were observed.

In 5 patients escaped beats of different origin were registered when the catheter was withdrawn through the infundibulum or the right ventricular cavity. Fig. 11 shows a case of supraventricular escaped beats observed when the tip of the catheter was withdrawn through the right ventricle. Immediately before, the original sinus rhythm had decreased from 90 to 65 beats per minute.

Disturbances in the heart action registered when the tip of the catheter was in the right auricle. In 80 of the patients who showed cardiac disturbances during the catheterization (91 per cent) electrocardiograms were taken when the tip of the catheter was situated in the right auricle. Eleven instances of irregularities in the heart action occurred in this group (11 per cent). Table 2 shows that ectopic contractions were not

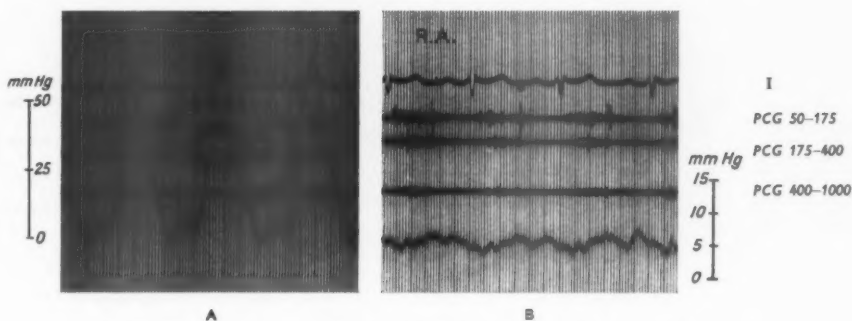


Fig. 12. Boy, aged 13 years. Diagnosis: Isolated pulmonary stenosis.

A. Original sinus rhythm of about 100 beats per minute registered when the tip of the catheter was withdrawn through the right ventricle. Loud systolic murmur up to 1000 cycles per second. Pressure about 60/0 mm Hg.

B. Supraventricular ectopic rhythm with the same frequency appearing when the catheter was withdrawn into the right auricle. The systolic murmur was unaltered. Pressure in the right auricle about 5 mm Hg.

registered as often as in the previous groups. All of them were of supraventricular origin. Ventricular tachycardia was not observed in a single case when the tip of the catheter was in the right auricle. Supraventricular and nodal rhythms, on the other hand, were noticed as transient phenomena in 2 and 3 cases, respectively. Fig. 12 gives an example of a case in which the function of the sinus node was replaced by a supraventricular ectopic pacemaker when the tip of the catheter was withdrawn through the right auricle.

In one case paroxysmal supraventricular tachycardia occurred when the tip of the catheter touched the endocardial surface of the right auricle (Fig. 15). Finally, in this group one case of a sino-auricular block and another of escaped beats were observed.

Disturbances in the heart action registered when the tip of the catheter was in the left side of the heart. In cases of septal defects the catheter could sometimes be introduced through them into the left side of the heart. Moreover, the material comprised 2 children with double superior vena cava, one entering into the right and the other into the left

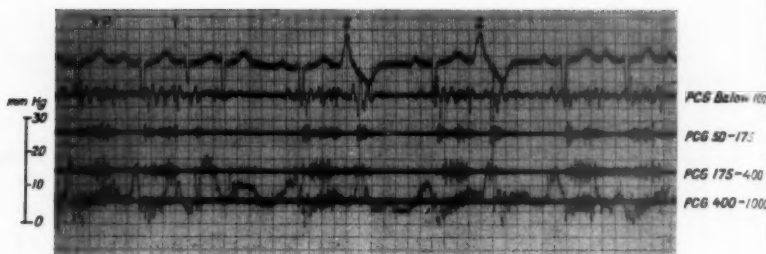


Fig. 13. Boy, aged 9 years. Diagnosis: Tetralogy of Fallot + atrial septal defect.

Tracings recorded when the tip of the catheter was placed in the pulmonary vein (course of the catheter: Right auricle — auricular septal defect — left auricle — pulmonary vein). The electrocardiogram shows one nodal, almost interpolated, extrasystole (1) and two right ventricular extrasystoles (2). Loud systolic murmur up to 1000 cycles per second corresponding to the normal contractions. Pressure about 15/8 mm Hg. Notice the diminishing of the systolic murmur during the premature beats.

auricle. In these 2 cases it was possible to catheterize all the chambers of the heart. Of the 88 children who showed cardiac disturbances during catheterization the left side of the heart could be reached by the catheter in 13 instances (15 per cent). Fifteen instances of disturbances in the heart action were observed in this group, indicating that these irregularities occurred as often as when the catheter was stimulating the right side of the heart (table 2). The left auricle and the pulmonary vein were reached by the catheter in 5 and 3 instances, respectively. In 10 cases the tip of the catheter could be inserted into the left ventricle and in 4 of these cases the tip was subsequently introduced into the aorta.

Table 2 shows that extrasystoles were the commonest arrhythmia produced by the catheter in the left side of the heart. Fig. 13 gives an example of extrasystoles of different origin registered when the tip of the catheter was situated in the pulmonary vein. Another case of single ectopic contractions and a run of left ventricular tachycardia is illustrated in fig. 14. In this case the tip of the catheter was slowly withdrawn from the aorta into the left ventricle.

In one case, a paroxysmal supraventricular tachycardia with a ventricular rate of about 300 beats per minute started when the

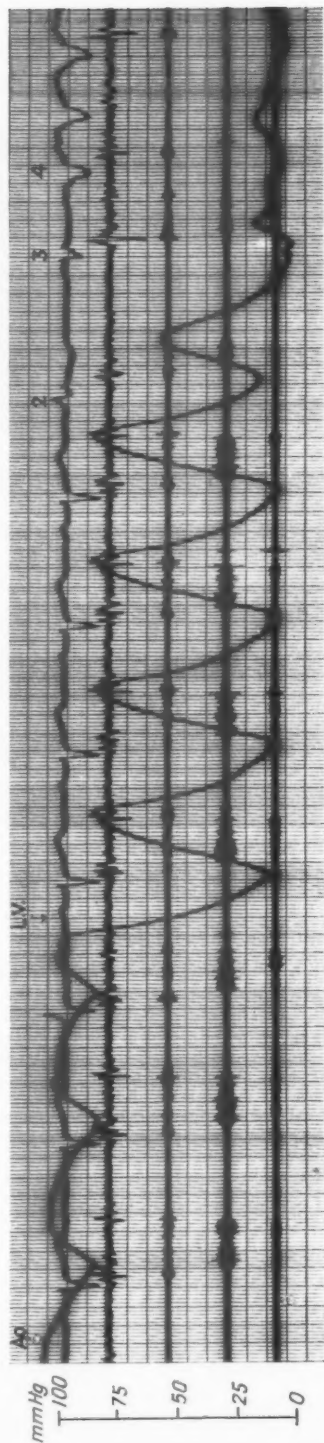


Fig. 14. Girl, aged 10 years. Diagnosis: Tetralogy of Fallot.

Tracing recorded when the tip of the catheter was withdrawn from the aorta (Ao) into the left ventricle (L.V.). Loud systolic murmur up to 1000 cycles per second. Pressure in the aorta about 110/75 mm Hg and in the left ventricle about 75/10 mm Hg (the pressure curve is slightly damped). ECG, lead I. PCG: Below 100, 50-175, 175-400, 400-1000 cycles per second, respectively.

One non-premature ectopic beat (1) was registered immediately before the tip of the catheter reached the left ventricle. On further withdrawal through the left ventricle a ventricular (right?) extrasystole (2) occurred followed by a supraventricular ectopic beat with pathological ventricular conduction. Immediately after that a left ventricular tachycardia started (4) which lasted for 29 beats. Notice the fall in the pressure and the diminishing of the systolic murmur during the premature contractions. When the catheter was withdrawn through the septal defect into the right ventricle the tachycardia stopped and apart from some extrasystoles no other disturbances in the heart action followed.



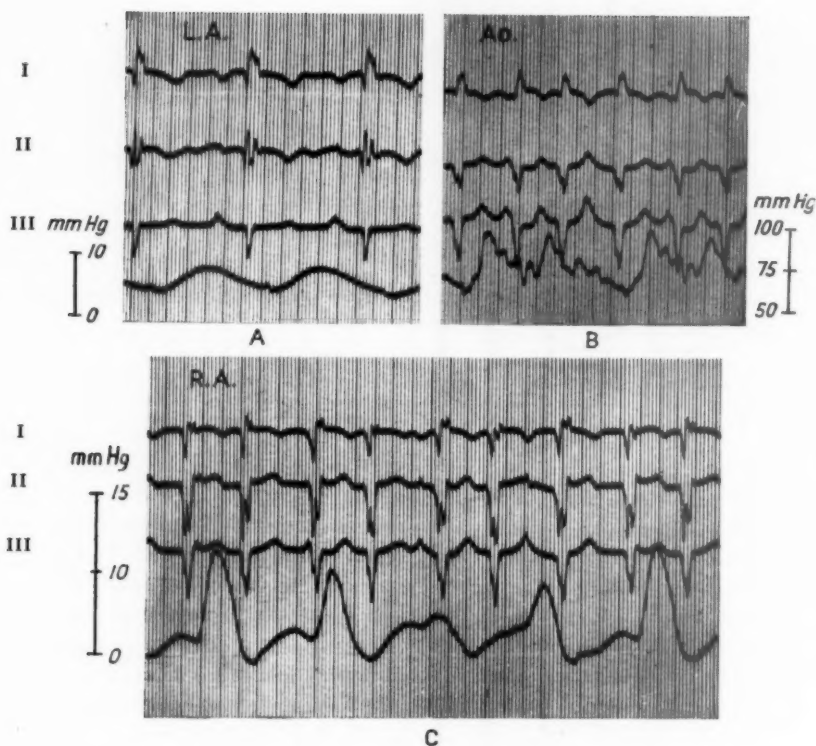


Fig. 15. Boy, aged 12 years. Diagnosis: Situs inversus. Tetralogy of Fallot + atrial septal defect.

A. Original sinus rhythm registered when the tip of the catheter was inserted through the atrial septal defect into the left auricle. The standard electrocardiogram shows a delayed intraventricular conduction. Pressure in the left auricle about 8/4 mm Hg.

B. Paroxysmal supraventricular tachycardia with a ventricular rate of 200 to 300 beats per minute arising when the tip of the catheter was inserted into the aorta (course of the catheter: right auricle — right ventricle — ventricular septal defect — left ventricle — aorta). Pressure in the aorta about 100/60 mm Hg. This tachycardia was continuously recorded on withdrawal of the catheter into the right ventricle.

C. When the tip of the catheter reached the right auricle a paroxysmal tachycardia of the same frequency but originating from another supraventricular focus started. Pressure in the right auricle about 10/0 mm Hg. This second attack of paroxysmal tachycardia continued until the catheter was removed from the heart.



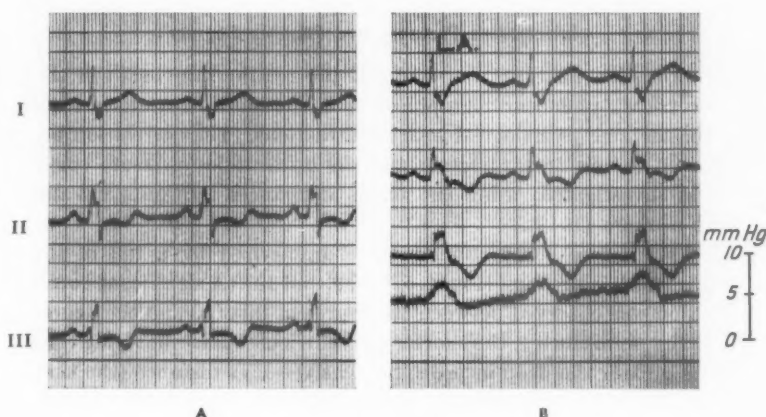


Fig. 16. Girl, aged 7 years. Diagnosis: Atrial septal defect.

A. Standard electrocardiogram before and after catheterization. Moderate right bundle branch block (QRS interval 0.08 second).

B. Increase of the bundle branch block (QRS interval 0.12 second) occurring when the tip of the catheter was inserted into the left auricle through the atrial septal defect. P-Q interval unaltered. Pressure in the left auricle about 8/5 mm Hg.

tip of the catheter was inserted into the aorta. This rhythm continued when the catheter was withdrawn through the left ventricle and an intraventricular septal defect into the right ventricle. On further withdrawal of the catheter into the right auricle a paroxysmal tachycardia of a different supraventricular origin appeared and it lasted until the catheter was removed from the heart (Fig. 15).

Among disturbances in the stimulus conduction, one case of an incomplete atrio-ventricular block occurred when the tip of the catheter touched the endocardial surface of the left ventricle.

In one case a right bundle branch block suddenly increased when the tip of the catheter was inserted through an intra-auricular septal defect into the left auricle. When the catheter was withdrawn into the right auricle the original intraventricular conduction was restored. (Fig. 16).

Finally, 2 cases of escaped beats were registered when the tip of the catheter was situated in the left ventricle and in the aorta.

### Intracardiac Pressure and Phonocardiogram

Detailed analysis was made of the relationship between the electrical, phonocardiographical and mechanical events during normal and pathological heart contractions. The correlation between the electrocardiogram and the intracardiac pressure curve was investigated, using the terms introduced by COBLENTZ and co-workers (1949).

Premature contractions were characterized by a fall of the intracardiac pressure (Fig. 4, 5, 6, 8, 9, and 14). A significant correlation was observed between the degree of this fall and the degree of the prematurity; the shorter the ventricular diastolic filling time the greater the drop in pressure. The Q—RVs distance (the time interval extending from the initial deflexion of the QRS complex to the beginning of the right ventricular systole) was also significantly correlated to the degree of prematurity. The prolonged Q—RVs interval which was found in markedly premature contractions might, according to COBLENTZ and co-workers, suggest a delayed contraction of the right ventricle. Premature contractions were also characterized by a diminishing of both the amplitude and the duration of the murmur. As a rule, this diminution occurred irrespectively of the length of the time interval between the premature beat and the succeeding beat (fig. 5, 6, 8, 13, and 14). Here, too, there was a significant correlation between the degree of prematurity and the degree of the diminishing of the murmur. On the other hand ectopic beats, which did not occur prematurely showed the same pressure curve and phonocardiogram as the normal beats (Fig. 7, 8, and 14).

The influence of tachycardias on the pressure curve and the phonocardiogram was principally the same as that of premature contractions, the main factor being the frequency, in other words the phase of the diastolic filling of the heart when the ectopic beats occurred (Fig. 8 and 12).

Supraventricular and nodal rhythms did not, as a rule, alter the pressure curve or the phonocardiogram if the heart rate was unaltered (Fig. 2 and 12).

In auricular flutter it was observed that heart cycles with

a higher degree of atrio-ventricular block and a relatively long ventricular filling time were followed by a higher pressure in the right ventricle and in the pulmonary artery than were cycles with a lower degree of block. Corresponding observations were made with regard to the change in the murmur. The auricular pressure tracing, on the other hand, seemed to be uninfluenced by the degree of the atrio-ventricular block.

In sino-auricular block there was no change in the pressure curve or phonocardiogram except for a "pause" corresponding to the dropped heart contraction.

Incomplete atrio-ventricular block without dropped beats did not alter the pressure curve or the phonocardiogram. In cases of complete atrio-ventricular dissociation it was observed that the rise in the right ventricular pressure took place at the expected time after the QRS complex (Fig. 9). The height of the auricular wave was variable, depending on the phase of filling of the right ventricle. In the phonocardiogram a complete dissociation between auricular and ventricular activity was registered.

Intraventricular blocks were characterized mainly by an increase in the QRVs interval. Escaped beats showed the same pressure curve and phonocardiogram as did the normal beats (Fig. 11).

### Discussion

Pathological disturbances in the heart action are relatively rare in children. Among 5,600 children examined at the cardiological department of Kronprinsessan Lovisa's Children's Hospital in 1945-46, only 126 (2.25 per cent) revealed pathological arrhythmias (LANDTMAN, 1947). Extrasystoles were the commonest disturbance (86 cases). The majority of the rest of the children presented arrhythmias due to disturbances in the stimulus conduction.

In the present investigation practically all known disturbances in the heart action could, as transient phenomena, be registered during catheterization. It is worth mentioning that many of these artificially produced arrhythmias, e.g. ventricular tachycardias (flutter), very seldom occur spontaneously in children.

Moreover, the ectopic contractions which did not alter the nomotopic rhythm are, as far as I know, not described in the paediatric literature (Fig. 7). From an electrocardiographical point of view they seem to represent an intermediate phenomenon between extrasystoles and escaped beats.

The disturbances in the heart action registered during catheterization were, in all probability, caused by the mechanical excitation produced by the catheter on the specific conduction system. The main bulk of this system is said to run subendocardially, whereas the myocardium and particularly the epicardial surface of the heart, contain this network to a smaller degree. It is, perhaps, due to this fact, that disturbances in the heart action are relatively difficult to produce by excitation of the pericardium. In 100 patients examined electrocardiographically during pneumonolysis, GROEDEL and BORCHARDT (1948) were able to produce premature contractions by mechanical excitation of the pericardial surface of the heart in only 3 instances. ZIEGLER (1948), on the other hand, recorded the electrocardiogram of 195 children submitted to operation for congenital heart disease. Arrhythmias due to increased cardiac irritability, including premature contractions and paroxysmal tachycardia, occurred during the operation in 21 patients. The conditions seem, however, to be more complicated with regard to the mode of origin of these arrhythmias in this last mentioned series. It is noteworthy that ZIEGLER did not observe any association between the arrhythmia registered and the nature of the heart disease.

In evaluating the causative factors of these artificially produced arrhythmias, the possible influence of the continuous drip through the catheter must be considered. The temperature of the physiological saline solution dropping through the catheter was about 15–20° C. In this connection it might be mentioned that HOFF and STANSFIELD (1949) observed ventricular tachycardia arising when the ventricle of a dog was locally cooled. It seems, however, very unlikely that the drop infusion would be an important factor in producing the cardiac disturbances, considering the fairly high temperature of the solution and the slow drop rate (about 20 drops per minute).

The fact that the majority of cardiac disturbances occurred when the catheter tip was stimulating certain limited regions of the endocardial surface, indicates that the ability of stimulus formation is different in different parts of the specific conduction system. Regions in which arrhythmias easily could be induced were the infundibulum of the right ventricle and the pulmonary artery, and furthermore, the endocardial surface of the rest of the right ventricular cavity. This suggests that the power of ectopic stimulus formation, under the prevailing conditions, were more pronounced in the peripheral ramifications than in the proximal parts of the specific system.

The marked contrast between the ease of inducing arrhythmias in the ventricle and the difficulty of inducing them in the auricle has been observed by many authors (BLOOMFIELD et al. 1946, BING et al. 1949, LEVINE et al. 1949, and others). In their investigations of the coronary blood flow, in which the tip of the catheter was all the time stimulating the endocardial surface of the right auricle, BING and co-workers very rarely observed arrhythmias arising. In view of the fact the atrio-ventricular node is situated close to the coronary sinus, this node seems to be relatively insensitive to mechanical stimulation.

Because of the difference in the excitability of the endocardium in different parts of the heart, it is possible that the usual site of ectopic stimulus formation are the peripheral ramifications of the specific conduction system and, more particularly, the network of Purkinje. As it is well known, extrasystoles are usually ventricular. Of spontaneous extrasystoles observed in 86 children, 52 were of peripheral ventricular origin (LANDTMAN, 1947).

With regard to the pathogenesis of cardiac disturbances, the investigation has revealed two main facts. First, that the same stimulus, that is the mechanical excitation produced by the catheter, can give rise to different kinds of disturbances. This indicates that the causative factors and mode of origin of different disturbances are not specific, in so far that the same excitation can cause disturbances both in the stimulus formation and in the stimulus conduction. The second fact is that mechanical stimulation of the specific conduction system in one part of the

heart might give rise to ectopic contractions originating from other parts, even from those which are situated on the opposite side of the septum.

It is difficult to explain the reason why the same mechanical excitation in some instances gave rise to ectopic contractions and in other to ectopic rhythms, tachycardias or flutter. It seems as if some localized regions of the conduction system possess a specific ability of producing a particular kind of arrhythmia. The fact that all the instances of ventricular tachycardia were observed when the tip of the catheter touched the endocardial wall of the right ventricle, and practically all cases of supraventricular ectopic rhythms occurred when the tip was stimulating the auricle, might speak in favour of this assumption. Individual characteristics with regard to the excitability of the conduction system might also explain the difference of reaction towards mechanical stimulation.

It seems reasonable to assume that the various blocks were caused by a slight mechanical compression, produced by the catheter, on the main branches of the conduction system. In one case a right bundle branch block appeared, when the tip of the catheter touched the septal wall of the right ventricle, and in another when the catheter was inserted through an auricular septal defect into the left auricle. In these positions the catheter might have slightly compressed the fibres of the right bundle of His. The chances of touching the main fibres of the conduction system with the catheter seem, however, to be small. When catheterization in one of these cases was performed again under the same conditions no block appeared.

It is remarkable, that excitation of one region of the specific conduction system in some cases gave rise to ectopic contractions originating from other parts of the heart. This was convincingly shown by the fact that out of 53 instances of ventricular extrasystoles produced by excitation of the wall of the right ventricle, 14 were of left ventricular origin. Moreover, of 18 instances of ventricular tachycardia arising from stimulation of the right ventricle, 8 originated from the left ventricle. Supraventricular ectopic contractions were also registered when the tip of the

catheter was in the ventricle. This phenomenon might, perhaps, be explained by the assumption that the stimulus impulse produced by the catheter was transmitted through the conduction system in a direction opposite to the usual spread of excitation, finally stimulating a focus with a high ability of stimulus formation. This is partly supported by the fact that left ventricular extrasystoles were more often registered when the catheter tip touched the septal region than regions distant from the septum. It is also possible, that the mechanical excitation had brought the conduction system into a state of hyperexcitability, facilitating the activity of ectopic foci. The possibility of the excitation having been transmitted to the opposite side of the heart by a reflex mechanism, via the cardiac nerves and the central nervous system might, perhaps, also be considered.

Many of the arrhythmias registered, particularly the multifocal tachycardias, are, when occurring spontaneously, generally considered as signs of severe myocardial damage (HOLZMANN 1945 and others). It is therefore remarkable, that an apparently harmless mechanical excitation of the specific conduction system, might give rise to exactly the same cardiac disturbances. The vast majority of the children, even those in whom tachycardias occurred, had no feeling of discomfort during the examination. But a few of them transiently complained of an uncomfortable sensation of pain in the chest or the epigastrium.

Although no complications of clinical importance were observed in these series, it seems advisable carefully to consider the indications before performing a heart catheterization.

### Summary

During heart catheterization of 142 children, of whom the majority had congenital heart disease, 160 cardiac disturbances were observed in 88 cases. None of the children revealed spontaneous arrhythmias before or after catheterization. The transient disturbances produced represented practically all known irregularities including ectopic contractions, tachycardias, ectopic rhythms, auricular flutter and irregularities due to disturbances in the



stimulus conduction. No complications of clinical importance were observed.

The majority of the disturbances were registered when the tip of the catheter touched the infundibulum of the right ventricle, and the pulmonary artery, and the endocardial surface of the rest of the ventricle. Thus, the smaller ramifications of the specific conduction system seem to possess the highest ability of ectopic stimulus formation. Cardiac disturbances were also registered in some cases where the tip of the catheter was inserted into the left side of the heart.

The disturbances were evaluated with regard to the electrocardiogram, phonocardiogram and the intracardiac pressure.

The results show that the mode of origin of cardiac disturbances is not specific, in so far that the same mechanical excitation could give rise of different disturbances, both in the stimulus formation and in the stimulus conduction. Moreover, an excitation of one part of the specific conduction system, could produce arrhythmias originating from other parts of the heart, even from those situated on the opposite side of the septum.

### Résumé

Lors du cathétérisme du cœur de 142 enfants, dont la majorité présentaient des malformations cardiaques congénitales, on a observé 160 perturbations cardiaques dans 88 cas. Aucun des enfants ne présentait d'arrhythmie spontanée avant ou après le cathétérisme. Les perturbations passagères produites représentaient pratiquement toutes les irrégularités connues, y compris les contractions ectopiques, la tachycardie, les rythmes ectopiques, les bourdonnements d'oreille et les irrégularités dues aux perturbations de la transmission du stimulus. On n'a pas observé de complications présentant d'importance clinique.

La majorité des perturbations ont été enregistrés quand la pointe de la cathéter a touché l'infundibulum du ventricule droit et l'artère pulmonaire ainsi que la surface endocardiale du reste du ventricule. Ainsi les ramifications plus petites du système spécifique de transmission semblent posséder la plus haute faculté de formation de stimulus ectopique. Des perturbations cardiaques



ont aussi été enregistrées dans certains cas quand la pointe de la cathéter a pu être introduite dans le côté gauche du cœur.

Les perturbations ont été évaluées par rapport à l'électrocardiogramme, au phonocardiogramme et à la pression intracardiaque.

Les résultats montrent que le mode d'origine des perturbations cardiaques n'est pas spécifique, dans ce sens que la même excitation mécanique a pu donner lieu à des perturbations différentes, tant en ce qui concerne la formation du stimulus que sa transmission. De plus, l'excitation d'une partie du système spécifique de transmission a pu produire une arrhythmie provenant d'autres parties du cœur, même de celles situées du côté opposé du septum.

### **Zusammenfassung**

Während der Herzkatheterisierung von insgesamt 142 Kinder, von welchen die Mehrheit ein angeborener Herzfehler hatte, wurden 160 Fälle einer Störung der Herztätigkeit bei 88 der untersuchten Kinder beobachtet. Kein einziges Kind zeigte eine spontane Arrhythmie weder vor noch nach der Herzkatheterisierung. Die durch die mechanische Reizung verursachten vorübergehenden Störungen umfassten praktisch genommen alle bekannte Formen einer unregelmässigen Herztätigkeit, wie ektopische Kontraktionen, Tachykardien, ektopische Rhythmusformen, Vorhofflattern und Störungen der Reizleitung. Es wurden keine Komplikationen von klinischer Bedeutung beobachtet.

Die Mehrheit aller dieser Störungen wurde registriert als die Spitze des Herzkatheters den Infundibulum des rechten Herzventrikels und der Pulmonalarterie oder die endokardiale Oberfläche des Restes dieses Ventrikels berührte. Es scheint somit als ob die feineren Verzweigungen des spezifischen Reizleitungssystems des Herzens die am stärksten ausgebildete Fähigkeit einer ektopischen Reizbildung besäßen. Störungen der Herztätigkeit wurden auch in einigen Fällen beobachtet, in welchen es gelang die Spitze des Katheters in die linke Herzhälfte einzuführen.

Die beobachteten Störungen wurden in Bezug auf das Elektrokardiogramm, das Phonokardiogramm und den intrakardialen Druck analysiert.

Die Ergebnisse zeigen, dass die Entstehungsweise dieser Herzstörungen nicht eine spezifische ist, da die selbe mechanische Reizung verschiedene Herzstörungen, sowohl die der Reizbildung wie die der Reizleitung, verursachen konnte. Eine Reizung eines Teiles des spezifischen Reizleitungssystems des Herzens konnte auch Arrhythmien produzieren, die ihren Ursprung in anderen, soeben auf der entgegengesetzten Seite des Herzseptums gelegenen Teilen des Herzens hatten.

### Resumen

Al sondear el corazón de 142 niños, cuya mayoría presentaba afecciones cardíacas congénitas, se han observado 160 perturbaciones cardíacas en 88 casos. Ninguno de los niños presentaba arritmia espontánea antes o después del sondeo. Las perturbaciones pasajeras producidas representaban prácticamente todas las irregularidades conocidas, y comprendían las contracciones ectópicas, la taquicardia, los ritmos ectópicos, los zumbidos del oído y las irregularidades debidas a las perturbaciones de la transmisión del estímulo. No se han observado complicaciones presentando importancia clínica.

La mayoría de las perturbaciones han sido registradas cuando el extremo de la sonda ha tocado el infundíbulo del ventrículo derecho y la arteria pulmonar, así como la superficie endocardial del resto del ventrículo. De esta manera las ramificaciones más pequeñas del sistema específico de transmisión parecían poseer la más alta facultad de formación de estímulo ectópico. Las perturbaciones cardíacas han sido registradas también en ciertos casos cuando el extremo de la sonda ha podido ser introducido en el lado izquierdo del corazón.

Las perturbaciones han sido evaluadas respecto al electrocardiograma, al fonocardiograma y a la presión intracardíaca.

Los resultados muestran que la forma de originarse las perturbaciones cardíacas no es específica, en el sentido de que la misma excitación mecánica ha podido dar lugar a perturbaciones diferentes, tanto en lo que concierne a la formación del estímulo como a su transmisión. Además, la excitación de una parte del

sistema específico de transmisión ha podido producir una arritmia que proviene de otras partes del corazón, hasta de aquellas situadas al lado opuesto del septum.

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## Unipolar Lead Electrocardiography in Congenital Heart Disease

By

CLAES-GÖRAN HERDENSTAM

In view of the slight attention accorded to Wilson's unipolar electrocardiography in pediatric literature, a brief report on the method and a preliminary presentation of the chief examination results obtained at Kronprinsessan Lovisa's Children's Hospital since the method was introduced here in 1947 seems to be called for.

The electrocardiogram can be described as a photographic reproduction of the electromotive forces which arise in the heart. The electrocardiograph serves as a sensitive galvanometer recording the difference in electrical potential between the two points on the surface of the body where the electrodes are connected. If the latter are placed on the limbs, as they are when the three standard leads are recorded, the electrocardiograph will register in, for example, Lead I the potential difference between the left arm (VL) and the right arm (VR). Similarly, Lead II involves the potential difference between the left foot (VF) and the right arm (VR) and Lead III the potential difference between the left foot and the left arm. Thus:

Lead I = Lead VL—VR

Lead II = Lead VF—VR

Lead III = Lead VF—VL

From this the conclusion may be drawn that a wave pointing, let us say, downward in Lead III can be produced if the potential in the left foot is either more negative or less positive than in the

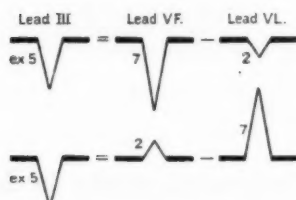


Fig. 1. Example of mathematical relation between standard leads and unipolar limb leads.

left arm. This means that an S wave in Lead III can be conditioned by either an S wave deeper in Lead VF than in VL or by an R wave higher in Lead VL than in VF (Fig. 1). Because of this GOLDBERGER (2) considers an ECG apparatus which records only the standard leads to be of as limited value as a blood pressure manometer which gives only the amplitude of the pulse: i.e. the difference between systolic and diastolic pressure.

Thus in order to understand the curve in a standard lead, it is desirable from both the theoretical and the practical points of view to be able to establish the real potential variations in the limbs, i.e. VR, VL, and VF. This has been rendered possible by the introduction into electrocardiography of a so-called indifferent electrode, by which is meant a comparative electrode the potential of which remains virtually constant throughout the heart cycle. If this electrode is connected to one pole of the electrocardiograph while its other pole is connected to a limb electrode, the ECG curve thus recorded can be considered to represent the true potential variations of the limb in question: i.e. VR, VL, or VF. Such an electrode was first described in 1934 by F. WILSON and co-workers (11), who created it by short-circuiting the limb electrodes via three high resistances of 5 000 ohms each (Fig. 2).

Regardless of the validity of Einthoven's equilateral-triangle theory, on which the proofs of the Wilson electrode's zero potential are based, a number of research workers, most recently DOLGIN and co-workers (1), have shown that we are justified, at any rate for all practical purposes, in regarding this as a true indifferent electrode. On this basis such a technique can, especially from the

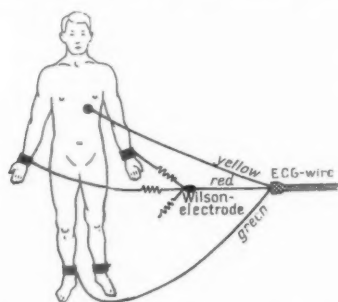


Fig. 2. Application of Wilson electrode. Apparatus: AB Elema Junior.

didactic point of view, be designated as unipolar . . . this in contrast to the standard ECG method, which is bipolar, with two electrodes about equidistant from the heart registering potential variations of equivalent amplitude. GOLDBERGER (2) has published a modification of the Wilson electrode. His electrode has no built-in resistances and is applied with broken connection to the limb where the test electrode is placed. By this means unipolar limb leads are obtained which he claims are of exactly the same form as when the Wilson electrode is used, although the amplitude is one and one half times as great ("augmented unipolar extremity leads"). Upon more careful analysis Goldberger's method seems, however, to be none too reliable in some respects, as has recently been pointed out by RAPPAPORT and WILLIAMS (7), among others. The lower the resistance employed in the central electrode, the greater the errors in method caused by the inevitable variations in the resistance of the skin under the three extremity electrodes. Hence if these are wholly eliminated, as in Goldberger's electrode, the variations in the resistance of the skin will influence the potential of the comparative electrode and thereby also that electrode's position as zero electrode. To obviate this source of error the Wilson electrode at our cardiologic laboratory was equipped from the beginning with resistances of 50 000 ohms each. Equally high resistances are used in the clinical apparatus recently put out by AB Elema.

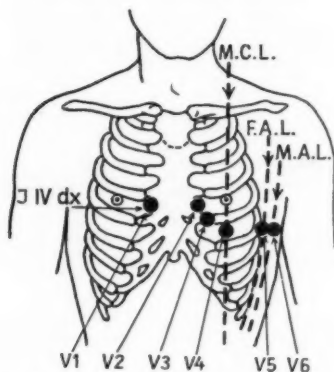


Fig. 3. Position of chest electrodes. MCL — medioclavicular line; FAL — anterior axillary line; MAL — midaxillary line.

In connection herewith it may be well to point out the importance of applying the electrodes satisfactorily. As a reliable indicator of this I used an EIC universal instrument to determine the resistance in ohms between the different extremity electrodes. As a rule it proved to be between 5 000 and 10 000 ohms following careful washing of the skin with alcohol, rubbing with a suitable electrode paste, and the use of silver electrodes. Without preceding washing with alcohol but with the same technique in other respects the resistance values were considerably higher, however — up to 50 000 ohms.

To record unipolar precordial leads the test electrodes are placed in six different places above the upper wall of the thorax (Fig. 3). In 1938 a special committee called this placing of the electrodes the most appropriate normal method for recording precordial leads (the Committee of the American Heart Association for the Standardization of Precordial Leads). According to WILSON and co-workers (12) Leads V1—V2 record the potential variations over the right ventricle and Leads V5—V6 the potential variations over the left ventricle, while Leads V3—V4 represent a “no man’s land” (the transitional zone) which is assumed to correspond to the interventricular septum. Recently ROSENBERG and AGRESS (8) showed that the six precordial Leads V1—V6



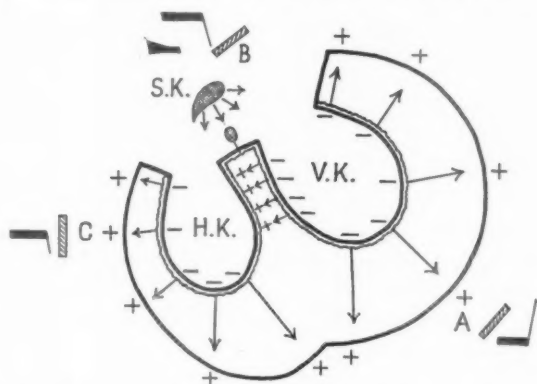


Fig. 4. Diagram showing spreading of excitatory process in ventricular section of heart. S. K. — sino-auricular node; V. K. — left ventricle; H. K. — right ventricle. A, B, and C signify three unipolar chest electrodes.

satisfactorily cover the anterior surface of the heart, from Lead V1, which lies above the right auricle, to Lead V6, which lies above the anterolateral portion of the left ventricle. In addition ROSENBERG and AGRESS (8) confirm the connection between the anatomical position of the septum and the localization of the transitional zone in the precordial electrocardiogram. As has been said, this is found normally in Leads V3—V4 but shows displacement to the right or left in ventricular hypertrophy, extremely rotated positions of the heart, and, according to ZIEGLER (13), when too much electrode paste is used or too large electrodes in pediatric practice. To exclude this last possibility I have used silver electrodes only 8 mm in diameter for the past year to record precordial leads in children.

In analysis of the details of the ECG curve in the unipolar limb and precordial leads, the following hypothesis given by WILSON and co-workers (12), among others, is of great practical value. When the electric impulse wave initiated by the sino-auricular node begins to spread centrifugally in the myocardium, the great mass of the ventricular musculature displays a positive potential while the ventricular cavity is negative (Fig. 4). Hence an electrode placed at A in Fig. 4 registers the positive potentials

in this heart phase and an electrode placed at B principally the negative, which gives rise to R or S waves, respectively, on the electrocardiogram. This may schematically be expressed thus: an electrode which sees the impulse wave from the front registers an R wave, while an electrode which sees the impulse wave from the back registers an S wave. When excitation is complete, i.e. when the impulse wave has passed through the whole ventricular wall and reached the epicardium under the chest electrode A in Fig. 4, the potential difference between resting and active cardiac muscle tissue is equalized. In that very moment the ECG curve shows a rapid, descending RS phase, Lewis's so-called "intrinsic deflection". The time at which this occurs, called V. A. T. (ventricular activation time) by SOKOLOV and LYON (10), is determined by measuring the time interval between the beginning of the Q wave and the maximum point of the R wave and is of practical value in diagnosing ventricular hypertrophy. An electrode placed at C in Fig. 4 simultaneously registers a lesser, positive potential from the right ventricular wall (sees the impulse wave from the front) and a larger, negative potential from the left ventricular wall (sees the impulse wave from the back), wherefore the electrocardiogram registers an S wave because of algebraic summation.

The foregoing interpretation of the origin of the unipolar curve has been criticized with regard to the exact electrophysiological basis by SCHAEFFER and TRAUTWEIN (9), among others, and has also proved unsatisfactory in the case of atypical hypertrophy reported below. Nevertheless it seems to permit of practical application in the majority of cases, and in experimental investigations carried out recently MEYER and HERR (6) worked out a very similar practical rule in spite of dissentient theoretical speculations. In these experiments it was noted that an impulse wave moving in the direction of the test electrode resulted in an R wave, while an impulse wave moving in the opposite direction gave rise to an S wave. MEYER and HERR (6) assumed further that the negative ventricle complexes usually found over the right precordium represented the spreading of the excitatory wave in a part of the heart distant from the right ventricle, such as the left ventricle or the posterobasal region.

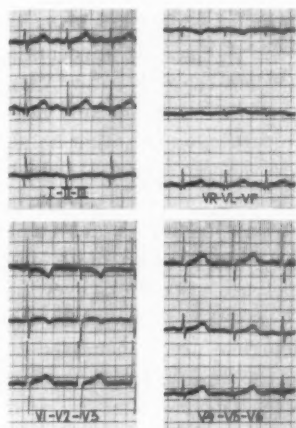


Fig. 5. ECG of a normal infant (girl aged 5 months).

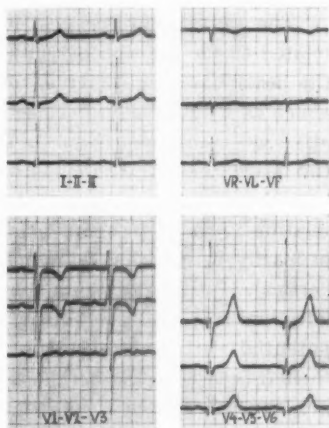


Fig. 6. Normal ECG from a 7 year old boy. Heart in semivertical position. El. axis  $+75^\circ$ .

The normal picture of the ECG in the six precordial leads varies with age, due to the fact that the relative dominance of the right ventricle characteristic of infants gradually disappears, to be replaced by the definitive physiologic left dominance. Thus one finds high R waves over the right precordium in all infants, as exemplified in Fig. 5. This circumstance in combination with the usually physiologically inverted T waves in children in Leads V1—V3 can cause diagnostic difficulties when there is a possibility of right ventricular hypertrophy. In somewhat older children with manifest preponderance of the left ventricle conditions are similar to those in adults except for the T wave changes over the right ventricle (Fig. 6). The QRS complexes here show low R and deep S waves over the right precordium together with high R and small S waves over the left. In addition distinct Q waves are normally registered in Leads V5 and V6, a circumstance which is assumed to indicate the initial negativity arising in the left ventricle as a result of the fact that the interventricular septum is activated primarily from the left branch of the bundle of His (Fig. 4).

The normal appearance of the unipolar extremity leads is related to the position of the heart in the thorax. In laevocardia the heart base negativity is concentrated in the right arm (VR), which as a result shows negative P and T waves and usually negative QS complexes (Fig. 6). In dextrocardia, on the other hand, the heart base negativity is projected to the left arm (VL), which is pathognomonic. With regard to the position of the heart in relation to its sagittal axis, there are three positions which come primarily in question: namely, the horizontal, intermediate, and vertical. With a horizontal heart the potential variations over the left ventricle are transmitted nearest the left arm, while the potential variations over the right ventricle are transmitted to the left foot (Fig. 7). With a vertical heart the situation is inverse: i.e., the left ventricle corresponds to the left foot and the right ventricle to the left arm (Fig. 6). Finally, with a heart in the intermediate position the potential variations in the left foot and left arm present a similar picture and generally correspond to the left ventricle.

The rotation of the heart around its longitudinal axis can be determined by studying 1) the unipolar limb leads and 2) the position of the transitional zone in the precordial leads. In extreme clockwise rotations (assuming that we regard the heart from the apex) this is localized in Lead V6 as a result of which the potential variations over the precordium have reference in such cases mainly to the right ventricle. In counterclockwise rotations we find the reversed situation with the transitional zone localized in Lead V1. As ROSENBERG and AGRESS (8) have pointed out, considerable clockwise rotation of the heart is usually found in right ventricular hypertrophy, in which the transitional zone is usually missing; thus the curve over the whole precordium corresponds most closely to the right ventricle (Fig. 11). In left ventricular hypertrophy, on the other hand, a sharp transitional zone is often recorded in Leads V3—V4, due to the fact that in this condition the interventricular septum is at right angles to the anterior thorax wall as a result of moderate counterclockwise rotation (Fig. 13).

The report below will serve merely to throw light on the

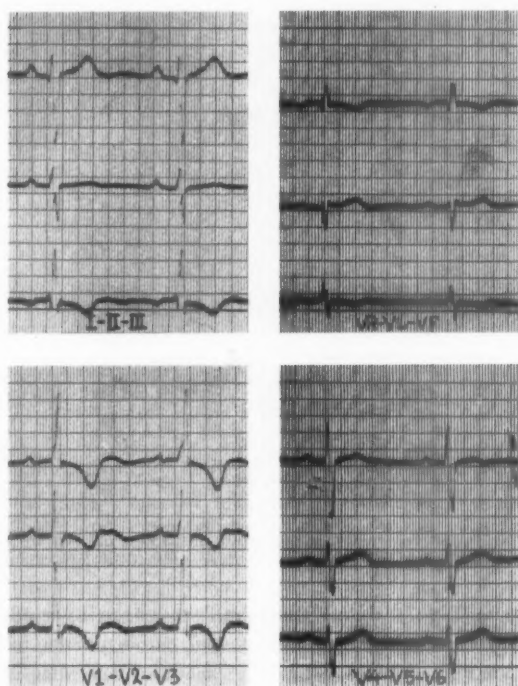


Fig. 7. Typical right ventricular hypertrophy in a 16 year old boy with tetralogy of Fallot. Heart in horizontal position. El. axis  $+155^{\circ}$  (pronounced right axis deviation).

principal ECG changes in ventricular hypertrophy and auricular enlargement in children with congenital cardiac malformations. A more detailed report on the appearance of the unipolar electrocardiogram in different cardiac malformations in children will be published later.

As far as the appearance of unipolar precordial leads is concerned, *right ventricular hypertrophy* can occur in either typical or atypical form. The former is characterized primarily by enlarged R waves over the right ventricle coming late in the somewhat prolonged QRS interval and by deepened S waves over the

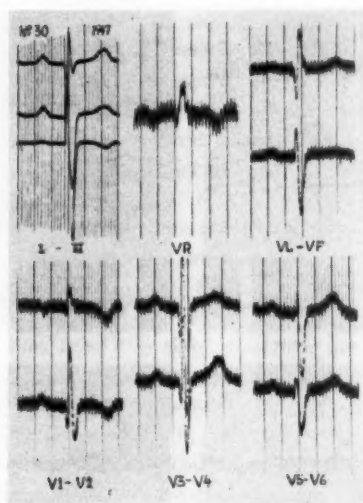


Fig. 8. Typical right ventricular hypertrophy in a 3 year old boy with tetralogy of Fallot. Heart in vertical position. El. axis  $-60^\circ$  (false left axis deviation).

left ventricle (Fig. 7). In addition the T waves are inverted over the right precordium, which, as has been said, can be normal in children but in pronounced cases, especially in connection with depressed S—T segments, might be interpreted as a sign of functional coronary insufficiency conditioned by right ventricular hypertrophy (HERDENSTAM 4 among others). In Lead VR enlarged R waves preceded by distinct Q waves are regularly recorded, while the ECG picture in Leads VL and VF varies with the position of the heart. Thus with a horizontal heart, which is usual in ventricular hypertrophy, the potential variations in Leads VL and VF correspond to those over the left and right ventricles, respectively, while the standard leads show right axis deviation (Fig. 7). With a vertical heart, on the other hand, which can occur in rare cases, the potential variations in Leads VL and VF correspond to those over the right and left ventricles, respectively, while the electric axis can show a "false" left axis deviation (Fig. 8). The delay of the "intrinsic deflection" which signifies ventricular hyper-

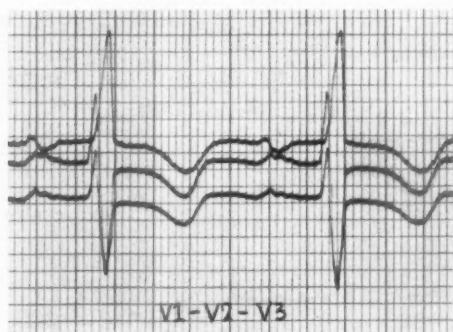


Fig. 9. Example of prolonged V. A. T. (ventricular activation time) in Lead V1 in typical right ventricular hypertrophy in a 14 year old girl with tetralogy of Fallot.

trophy is demonstrated in Fig. 9. Here the R wave comes about 0.04 seconds later in Lead V1 than in Lead V3.

Atypical right hypertrophy is characterized particularly by much deepened S waves over the right precordium. In a number of these cases the standard leads also display a strange appearance with similar RS complexes consisting of low R and deep S waves. According to GOLDBERGER and SCHWARTZ (3) this type of RS complex occurs in both right ventricular hypertrophy and infarcts. As there is seldom any question of the latter in children, in these cases of atypical right ventricular hypertrophy we have a valuable aid in the appearance of the standard ECG. In other cases with normal QRS complexes in Leads I—III the atypical ECG picture in the precordial leads cannot be distinguished with certainty from the picture in atypical left ventricular hypertrophy (cf. Figs. 10 and 12). Thus in Fig. 10 one finds S waves as deep as 6.5 mV in Leads V1—V2 and notched QRS complexes in the extremity leads but nothing definitely pathological otherwise. This ECG is from an 11 year old girl with the tetralogy of Fallot who died following a Blalock-Taussig operation. Autopsy revealed marked hypertrophy of the right ventricle.

Fig. 11 shows a case of marked right ventricular hypertrophy in a 9 month old girl whose heart showed very pronounced clock-

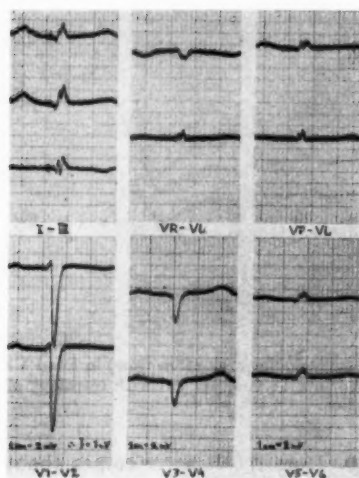


Fig. 10. Atypical right ventricular hypertrophy in an 11 year old girl with tetralogy of Fallot. No definitely established deviation of el. axis.

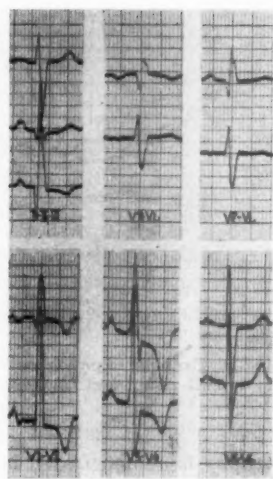


Fig. 11. Marked right ventricular hypertrophy in a clock-wise-rotated heart in horizontal position in a 9 month old girl.

wise rotation. The much enlarged R waves and the marked ST and T changes were recorded over most of the precordium (cf. Fig. 7). Because of the rotation, the potential variations over the left ventricle were transmitted to Lead VL, i.e. the left arm.

Electrocardiographically *left ventricular hypertrophy* also appears in typical or atypical form. In the former, deepened S waves are registered over the right precordium and enlarged R waves with delayed intrinsic deflection over the left (Fig. 13). In typical left hypertrophy the S—T segments are usually somewhat elevated in Leads V1—V3 and depressed in Leads V4—V6, in which latter leads the T waves are usually inverted as well. The frequent, marked U waves in Leads V2—V4 seems to constitute a further criterion of left ventricular hypertrophy; these are shown in Fig. 12. As in right ventricular hypertrophy, the appearance of the extremity leads is related to the position of the heart in the thorax. Hence when the heart is in a vertical position, with the left ventricle projecting toward the left foot and the right ventricle toward



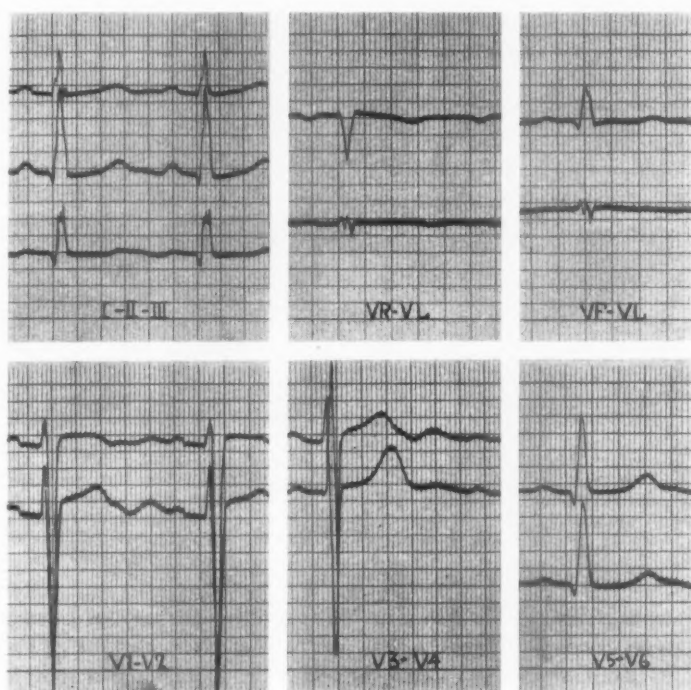


Fig. 12. Atypical left ventricular hypertrophy in a 6 year old boy with patent ductus arteriosus and coarctation of the aorta. Semivertical heart. El. axis  $+62^\circ$ . S waves in Lead V1—8 mV.

the left arm, one can in exceptional cases find a false right axis deviation.

In atypical left hypertrophy, as in atypical right hypertrophy, considerably deepened S waves registered over the right precordium are the only important pathological findings (Figs. 12 and 16). The marked U waves in Leads V2—V4 which appear fairly regularly in left ventricular hypertrophy usually make an electrocardiographic differential diagnosis possible, however (cf. Figs. 10 and 12).

Accurate analysis of the size of the cardiac ventricles along

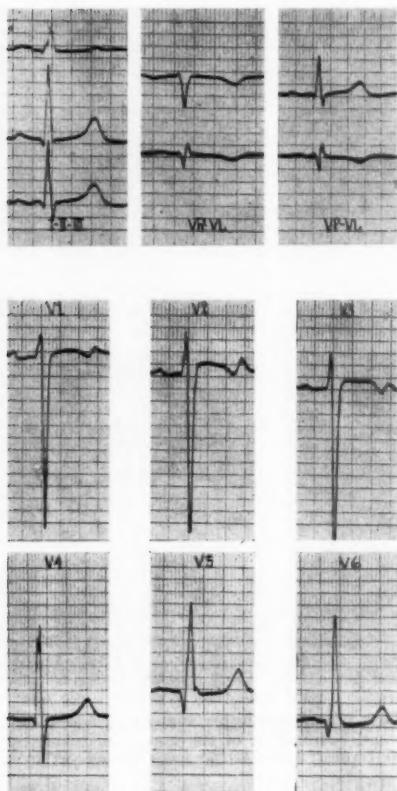


Fig. 13. Marked left ventricular hypertrophy in a 12 year old boy with patent ductus arteriosus 47 mm in circumference. Semivertical heart. El. axis  $+76^{\circ}$ . S waves in Lead VI—7.2 mV.

the lines indicated above is of considerable prognostic value, for example in cases of patent ductus arteriosus. In uncomplicated, moderately wide ductus with good operative prognosis, little or no left ventricular hypertrophy is recorded. In so-called "malignant" ductus arteriosus, with pronounced aortic-pulmonary shunt and the considerably increased burden on the left heart associated therewith, on the other hand, the electrocardiogram reveals pro-

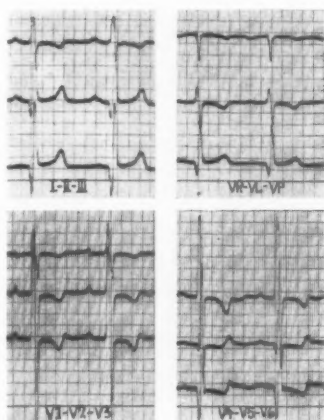


Fig. 14. Marked left ventricular hypertrophy and moderate right ventricular hypertrophy in a 13 year old girl with patent ductus arteriosus 60 mm in circumference. Heart vertical. El. axis  $+87^{\circ}$ .

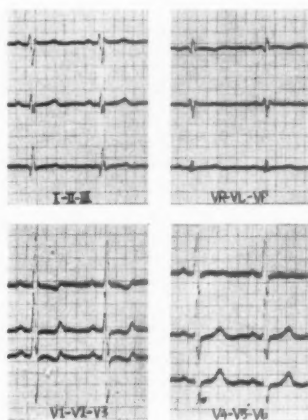


Fig. 15. Marked right ventricular hypertrophy in a 12 year old girl with patent ductus arteriosus 62 mm in circumference. Heart probably in horizontal position. El. axis  $+120^{\circ}$ .

gressive left ventricular hypertrophy. A case of this type is shown in Fig. 13, from a 12 year old boy with a patent ductus arteriosus 47 mm in circumference. The unipolar leads show marked left ventricular hypertrophy. At a later stage the "malignant" ductus arteriosus types also cause progressive right ventricular hypertrophy as a result of the increasing blood flow to the lungs and the consequent increase in pressure in the pulmonary artery, which also predisposes the patient to develop a secondary pulmonary sclerosis. Fig. 14 shows the ECG picture in a patent ductus arteriosus of this type with a circumference of about 60 mm; there is pronounced left hypertrophy with signs of functional coronary insufficiency and moderate right hypertrophy. This ECG diagnosis was later verified at autopsy. A cross section of the left ventricular wall measured 16 mm and one of the right 11 mm. The final stage in the "malignant" ductus arteriosus types is consequently a cor pulmonale, exemplified in Fig. 15. This ECG is from a 12 year old girl with a ductus 62 mm in circumference. It shows a marked

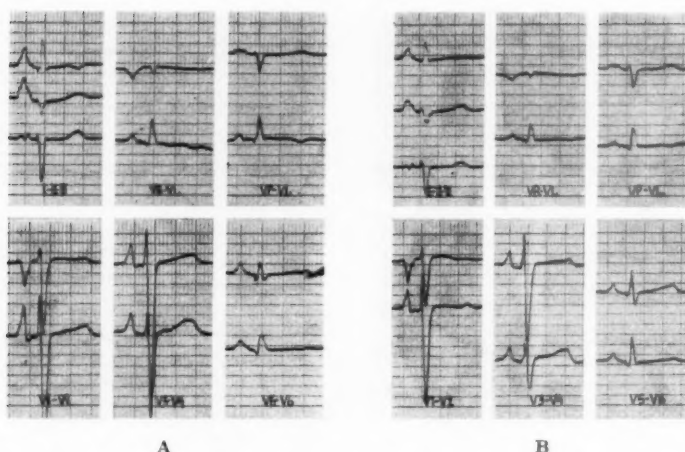


Fig. 16. Atypical left ventricular hypertrophy and very severe right auricular enlargement in a 4 year old boy with tricuspid atresia. A — before Blalock-Taussig operation. B — 1 month after operation.

right ventricular hypertrophy which was verified at autopsy. Autopsy also revealed pronounced secondary pulmonary sclerosis.

With regard to auricular enlargement, the Wilson ECG makes possible a considerably more accurate analysis of the P waves than is permitted by the well known division into P-mitrale and P-pulmonale of standard electrocardiography. As has been said, the electrode V1 lies immediately outside the right auricle, wherefore the voltage of the P waves is normally higher over the right precordium than over the left (Fig. 14). In one-sided auricular enlargement heightened, broadened, and pointed P waves are registered over the part of the precordium in question. Thus in Fig. 16 one finds markedly enlarged P waves of pathological form in Leads V1—V3, indicating severe right-sided auricular enlargement, a diagnosis confirmed by angiocardiography. In addition Fig. 16 shows considerable post operative reduction of the amplitude of the P waves from 1 to 0.5 mV in Lead II, which according to a previous study (HERDENSTAM and MANNHEIMER 5) can be interpreted as a sign of decreased auricular congestion.

### Summary

Following a short report on the method and its application in pediatric practice the author describes the appearance of the Wilson unipolar electrocardiogram in ventricular hypertrophy and auricular enlargement in children with congenital heart disease. The possibilities of diagnosing right or left ventricular hypertrophy by electrocardiographic means and thus of forming a valuable general conception of the nature of the cardiac malformation are demonstrated, with particular reference to cases of patent ductus arteriosus.

### Résumé

Après un bref rapport sur la méthode et son application chez les enfants, l'auteur décrit la manifestation de l'électrocardiogramme unipolaire de Wilson dans l'hypertrophie ventriculaire et la dilatation auriculaire chez des enfants ayant une maladie de cœur congénitale. Il démontre les possibilités de diagnostiquer l'hypertrophie du ventricule droit ou gauche à l'aide de l'électrocardiographie et de se former ainsi une idée générale de la nature de la malformation cardiaque, et se réfère particulièrement à des cas de canal artériel manifeste.

### Zusammenfassung

Nach einer kurzen Beschreibung der Methode und ihrer Anwendung in der Pädiatrie beschreibt Verfasser das Aussehen des unipolaren Wilson-Elektrokardiogramms bei Kammer- und Vorhofvergrößerung bei Kindern mit kongenitalen Herzfehlern. Die Möglichkeiten, durch Elektrokardiographie eine recht- oder linksseitige Ventrikelhypertrophie zu diagnostizieren und dadurch eine wertvolle allgemeine Auffassung von der Natur der Herzmissbildung zu erhalten werden demonstriert, wobei besondere Rücksicht auf Fälle von offenstehenden Ductus Botalli genommen wird.

### Resumen

Después de un breve informe sobre el método y su aplicación en los niños, el autor describe la manifestación del electrocardiograma unipolar de Wilson en la hipertrofia ventricular y la dilata-

ción auricular en los niños que padecen una enfermedad congénita de corazón. Demuestra las posibilidades de diagnosticar la hipertrofia del ventrículo derecho o izquierdo con la ayuda de la electrocardiografía, y de formarse así una idea general de la naturaleza de la malformación cardíaca, y se refiere particularmente a casos de "ductus arteriosus" manifiesta.

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## **Congenital Spastic Paralysis Treated with Parpanit**

by

**TORBEN JERSILD**

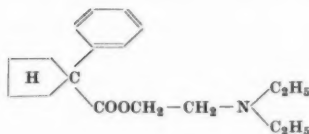
Parpanit is a synthetic spasmolytic substance produced by GEIGY in Switzerland. GRUNTHAL (1946) showed that in healthy subjects Parpanit acted on the proprioceptors, and also found that it had a favourable effect in the treatment of parkinsonism. HARTMANN (1946, 1947), BICKEL and DUBOIS (1947), and SCHWAB and LEIGH (1948) also found that Parpanit had a favourable effect on parkinsonism. DUNHAM and EDWARDS (1948), on the other hand, found that it had no better effect than the tropa-alkaloids.

In 1947 I had the opportunity to see, at the Scandinavian—Swiss Congress, a film demonstration of the good results which the Swiss had obtained with Parpanit in the treatment of a series of patients with parkinsonism. I was able to bring some of the substance home, and have since treated several patients with paralysis agitans and observed a definite effect on the muscle rigidity, intention tremor, and salivation.

Parpanit has not yet — as far as I know — been used in pediatrics, but it was natural to try its use in cases of congenital spastic paralysis, the symptomatology of which often includes evidence of damage to the extrapyramidal system.

### **Chemistry**

Its chemical formula is not unlike that of the closely related spasmolytic substances Trasentin and Dolantin. Parpanit is a diethylaminoethylester of phenylcyclopentancarboxylic acid.



### Pharmacology

Parpanit is most nearly related to the atropine group of drugs.

#### Action

Not much is known about the mode of action of Parpanit. Animal experiments have shown that it acts on smooth muscle: spasm induced in rabbit intestine with acetyl choline can be relaxed with Parpanit.

Animal experiments have further shown that Parpanit has a curarelike action on *striped* muscle.

Investigations in healthy human subjects have shown that it also acts on the *proprioceptors*.

In addition, Parpanit is believed to have a *central action* on the basal ganglia, which belong to the extrapyramidal system.

Like atropine, Parpanit inhibits the *cholinergic nervous system*. Thus the secretion of sweat and saliva is reduced, but in this respect Parpanit is 700 times weaker than atropine, which is a definite advantage, since patients do not get dry mouths with therapeutic doses of Parpanit. There may also be a slight fall in blood pressure and a slow pulse.

Indirectly, Parpanit has also a considerable psychological effect, the patient's self-confidence increasing as the tremor and rigidity diminish.

### Side-Effects

The main disadvantage of Parpanit treatment is giddiness, though this disappears in most cases if the treatment is continued. Some patients lose their appetites. Too large doses can cause tiredness and muscular weakness, an effect which is reminiscent of curare.



### Case Histories

Boy aged 7 years. No. 323/48. Admitted to the Pediatric Department of the Rigshospital March 30—July 29, 1948, and again Sept. 18, 1948. Diagnosis: congenital encephalopathy (Little's disease). First of three siblings, others healthy. No similar disorder in the family. Birth on expected delivery date (but birth weight suggested about six weeks premature), easy normal delivery, four and one-half hours, head presentation, birth weight 1650 g; asphyxiated for one-half hour. No K-vitamin treatment of mother or child. Both mental and physical development of child slow. Began to talk at 5 years.

*Physical Examination.* Pale and small. Speech almost incomprehensible. *Mentally* backward, but less than apparent at first, since he had difficulty in getting out his words. *Cranium* normal. *Pupils* normal. Nystagmus and squint. Extremities thin, with poorly developed muscles. Muscle tone constantly increased. Finger-nose test: movements very uncoordinated, marked intention tremor and athetoid movements (thus could not hold picture book still, much less the pages).

*Lower Limbs:* internally rotated, adducted, with marked bilateral clubfoot. Marked scissor gait on attempting to walk; unable to stand or walk alone. Patellar reflexes increased; they can produced obtained from the anterior surface of the whole tibia. Bilateral clonus and Babinski.

*Posture:* sat unsteadily with very rounded back, holding tightly to seat and letting head drop when lifted by the upper trunk.

*Investigations.* Radiography of cranium normal. Lumbar puncture normal. WR negative. Blood examination normal. Rh positive (mother Rh positive). Intelligence test: could not be assessed numerically, as nearly half of the tests could not be used because of his poor motor and speech functions. Mental age between 2 and 3 years. Most of what he said was incomprehensible.

*EEG.:* moderate disrhythmia, marked frequency changes in all leads and too much slow activity, especially occipitally. No differences between the two sides.

*Treatment.* Treated in the Rigshospital, first with vigorous physical treatments and in the last three months with very active exercises, with great emphasis on the patient's cooperation. With these there was some improvement, particularly in his behaviour and psychological development. However, there was no change in the rigidity, intention tremor, nystagmus, salivation or clonus (clubfeet and scissor-gait quite unchanged).

On Nov. 26 Parpanit treatment was begun, 6 mgm given three times a day, increasing by 6 mgm every day to 40 mgm (3/4 tabl. Parpanit fort.) three times a day. It was soon evident that the doses were

too big; the child was tired, apathetic, and lost his appetite. The dose was reduced to 1/2 tablet three times a day and the treatment continued for four weeks. After one week there was a marked reduction of the tremor, the athetosis movements stopped, and the nystagmus, rigidity, and salivation showed marked improvement. After four weeks he could walk in a walking chair almost without scissoring, and the clubfoot position had almost disappeared. He could carry a spoon to his mouth and put seven bricks on top of one another and straighten them with his left hand without knocking them over. The nystagmus had disappeared completely. He lay quite still and read his picture book.

On the other hand the signs of damage to the pyramidal system, the foot clonus, the increased patellar reflexes, and the positive Babinski were unaffected.

For the last eight weeks the patient has not been treated with Parpanit, and in contrast to the patients with parkinsonism whom I have treated, the condition was nearly stationary for six weeks. In the last 14 days the tremor, athetosis, and salivation have returned.

Apart from this patient, a further 3 children with congenital spastic paralysis have been treated. In 1, who had exclusively spastic signs of the lower limbs, the drug had no effect, while the other 2, who also had extrapyramidal lesions, have responded well to Parpanit treatment.

I believe that in this country we have not been sufficiently active in treating congenital spastic paralysis. In America and England progress is more advanced: special departments with large staffs of specially trained doctors, masseuses, and teachers have been set up for the treatment of these patients.

Parpanit does not, of course, supersede other treatments, but I myself do not doubt that these children can be greatly helped by a combination of educational and psychological, physical, orthopedic, and medical treatment, preferably centralized.

In recent years the Pediatric Department of the Rigshospital has adopted a more active training of children with sequelae of encephalopathies acquired early in life. Particular emphasis has been laid on the conscious cooperation of the children in this active training, which is adapted to suit each case. Psychologically, it is important that too great, rather than too small, demands be made on these children (Carlson, 1941).

### Summary

A brief account of the chemistry, pharmacology, and mode of action of Parpanit is given, and 4 cases of Little's disease treated with this drug are reported. Three of these, who had extrapyramidal disturbances in addition to spasticity, responded well to the treatment, while 1, who had spasticity alone, was not affected.

Parpanit treatment does not supersede other treatments of Little's disease, but in suitable cases it is a valuable supplement.

### Résumé

Bref rapport de la chimie, pharmacologie et mode d'action du Parpanit et compte rendu de 4 cas de la maladie de Little. Trois d'entre eux, qui présentaient des troubles extra-pyramidaux outre des phénomènes spastiques, répondaient bien au traitement, tandis qu'un cas qui présentait seulement des troubles spastiques, n'était pas affecté.

Le traitement par le Parpanit ne doit pas supplanter les autres traitements de la maladie de Little, mais peut, dans certains cas, être un précieux supplément.

### Zusammenfassung

Ein kurzer Bericht über Chemie, Pharmakologie und Anwendungsweise des Parpanit, sowie Schilderung von 4 damit behandelten Fällen der Littleschen Krankheit. Drei von diesen, welche zusammen mit Spasmen auch extrapyramidale Störungen zeigten, reagierten gut auf diese Behandlung, während ein Fall, der nur spastische Erscheinungen aufwies, nicht beeinflusst wurde.

Parpanitbehandlung kann eine andere Behandlung der Littleschen Krankheit nicht ersetzen, ist aber in entsprechenden Fällen eine wertvolle Ergänzung.

### Resumen

Se da una breve reseña de la química, farmacología y modo de acción del Parpanit, y se describen cuatro casos de la enfermedad de Little tratados con esta droga. Tres de ellos, que

sufrían molestias extrapiramidales además de la espasticidad, respondieron bien al tratamiento, mientras que uno que presentaba solamente espasticidad no fué afectado.

El tratamiento con Parpanit no reemplaza a otros tratamientos de la enfermedad de Little, pero en casos apropiados es un valioso suplemento.

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## Procaine Penicillin Therapy in Scarlet Fever<sup>1</sup>

By

TORBEN JERSILD and JOHN MUNCK

The discontinuous penicillin treatment (*i.e.*, 60 000—150 000 I. U.  $\times$  2 daily for six days) has been employed during the last two years for the treatment of scarlet fever in the Blegdam Hospital, and the results obtained with this form of penicillin therapy come fully up to the results obtained by several injections daily (5, 6).

A further reduction in the number of injections cannot be said to be of particular importance to the hospital treatment of scarlet fever, as the two injections a day neither make too heavy demands on the capacity of the personnel nor cause any particular inconvenience to the patients. On the other hand, treatment with merely one injection a day would be of great significance to the home treatment of scarlatina, and if this should prove practicable, it is reasonable to assume that the number of patients admitted to the hospital for this disease might be reduced considerably.

An attempt to reduce the number of injections of ordinary penicillin to one a day with unaltered daily dose showed that this measure was not sufficiently effective. JERSILD (7) treated 26 patients in this way. When the treatment was discontinued hemolytic streptococci were found to be present in 58 %, and 6 patients had altogether 11 complications.

It is obvious, therefore, that this form of treatment requires penicillin preparations giving a more continuous rise in the penicillin concentration in the blood and tissues, and in procaine penicillin (PP) we have obtained such a preparation.

<sup>1</sup> The investigation has been supported by the «Kong Christian den Tien-des Fond».

In the Blegdam Hospital (7) we have treated 39 scarlatinal patients with PP, 180,000—240,000 I. U. once a day for six days. After the treatment was discontinued hemolytic streptococci were found in only 2 patients, and only 2 patients had complications (adenitis and tonsillitis, respectively).

PP is a salt of one molecule penicillin and one molecule procaine (BOGER (1), HERRELL (4), SALLIVAR (9), SULLIVAN and associates (8)). It is a slowly soluble compound which releases penicillin after the injection but slowly. The preparation is suspended in sesame oil containing 300,000 I. U. per ml. The amount of procaine is 125 mg per 300,000 I. U. penicillin. The preparation is somewhat troublesome to deal with as it has a tendency to clump in the syringe, even when heated before using. Although procaine here is combined into a salt, it still seems to have preserved some anesthetic action, as the injections are said to be less uncomfortable than ordinary penicillin.

PP, in contrast to bee's wax-oil preparations, gives no inconvenience. In the 200 cases we have treated with PP we have not observed any local reactions or general toxic manifestations whatever.

The blood penicillin concentration after a single injection of 300,000 I. U. PP is evident from Fig. 1, from which it will be noticed that after eight hours a concentration of  $> 0.1$  I. U. per ml was found in all the patients. After 12 hours about one half of the patients showed a concentration of  $> 0.1$  I. U. per ml. This concentration is fully sufficient *in vitro* to inhibit the growth of the hemolytic streptococci.

To ascertain the rational penicillin dosage in scarlet fever it would be of great value to know the period of penicillin activity required for destruction of the hemolytic streptococci. In experiments *in vitro*, performed in the Blegdam Hospital, we have found that the time required for sterilization of a serum broth culture of hemolytic streptococci varies from 3 to over 48 hours, depending on the size of the bacterial inoculum. This circumstance is known also from other experimental series, and as in scarlet fever we are unable to estimate the amount of bacteria present, this possibility is out of the question.

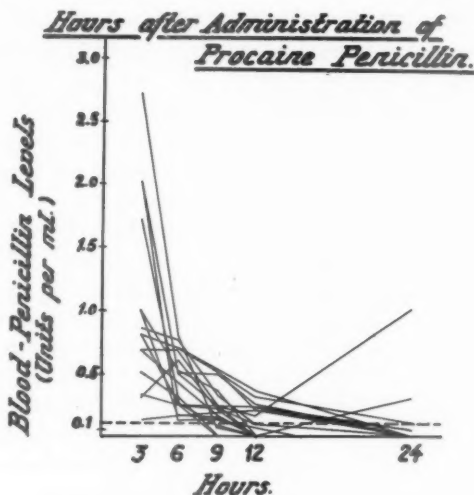


Fig. 1.

In order to investigate PP<sup>1</sup> therapy in scarlet fever, we have treated 200 patients with the following doses:

0—1	year:	120,000 I. U.	intramuscularly	×1	for 6 days
1—5	years:	180,000 I. U.	»	»	»
6—15	»	: 240,000 I. U.	»	»	»
over 15	»	: 300,000 I. U.	»	»	»

For the sake of control observation it would, of course, have been preferable to have the patients hospitalized for four weeks, but for want of space this idea had to be given up — in particular in view of our present knowledge concerning the now prevailing period of treatment for scarlet fever. In uncomplicated cases the patients were discharged after seven—eight days and told to return for ambulatory control examination four and six weeks later. At both examinations cultures were made from the patients

<sup>1</sup> The procaine penicillin preparation was kindly placed at our disposal by "Løvens kemiske Fabrik", Copenhagen, which also has determined the blood penicillin concentration in the patients.

Material .....	JER-SILD	JER-SILD	FLAUM	STRØM	BØE	JER-SILD	JER-SILD	JERSILD & MUNCK
No. of pts. ....	200	200	240	225	100	150	26	200
Preparation .....	S	P-A	P-A, P	P	P	P	P	P-P
Inj. per day .....		3	3-6	8	8	2	1	1
Weeks in hospital .....	4	4	2	4-6	1	2-4	3	1
+ hemolytic streptococci (%)								
before treatment .....	69	74	100	76	81	79.7	53.8	60.5
After 3 days .....	65	7			19	6.8	19.2	3
" 5 " .....	60	2		2				
At discontinuance of treatment	73	4	10	} 21.8		3.4	57.7	1.5
After 4-6 weeks .....	53	3				11		5.5
" 6-8 " .....						12.8		10

Explanation of symbols: S = sulfanilamide, P = penicillin, P-A = penicillin adrenalin, P-P = procaine penicillin.

Fig. 2.

for hemolytic streptococci. In addition, at the first examination the antistreptolysin titer and the sedimentation rate were also measured. The urine was examined at both examinations. Upon discharge the patients were instructed to consult us at once if any illness appeared.

The age distribution of this material was as follows:

1 year .....	2 patients
1—5 years .....	116 "
6—10 " .....	62 "
11—15 " .....	16 "
16—20 " .....	0 "
21—25 " .....	2 "
26—30 " .....	0 "
31—35 " .....	2 "
Total .....	200 patients

The culture results constitute a very important criterion as to the effect of antibiotics in scarlet fever. These results are presented graphically in Fig. 2, in which our material is compared to other materials treated with sulfanilamide or with ordinary penicillin with a varying number of injections per day.



From Fig. 2 it is evident that our results are quite as good as those obtained in other materials with two or more injections of ordinary penicillin per day, whereas treatment with ordinary penicillin once a day is far from giving as good results (7).

Upon discontinuance of the PP treatment only 1.5 % of the patients were streptococcus-positive.

Of the 11 streptococcus-positive patients revealed by cultivation at the first ambulatory examination 2 had had purulent rhinitis prior to the examination and nasal cultures showed growth of hemolytic streptococci; 2 had had tonsillitis; and 2 were later readmitted with scarlatinal infection, only one of whom had been positive at the first ambulatory examination.

Of the 20 streptococcus-positive patients disclosed by the second ambulatory examination, 11 had had complications in the course of their illness.

Those patients who failed to return for the follow-up examination were examined at home (secondary tonsillitis was ascertained in 6, purulent rhinitis in 2, otitis media in 3).

On admission, 139 patients (69.5 %) yielded growth of hemolytic streptococci, showing the following type distribution:

Group A Type	1:	1 patient
» A »	4:	79 patients
» A »	22:	8 »
» A »	25:	1 patient
» A »	28:	1 »
» A »	X:	40 patients
Several types:	9	»

Another important criterion of the effectivity of the therapy in scarlet fever is the frequency of complications. This is presented graphically in Fig. 3.

All our patients were under observation up to six weeks after the day of admission.

There were 3 cases of suppurating otitis media after discharge of the patient from the hospital. Two of these patients were readmitted and both yielded growth of hemolytic streptococci in ear cultures. The third one failed to return for the reexamina-

Material .....	JER- SILD	JER- SILD	FLAUM	STRÖM	BØE	JER- SILD	JER- SILD	JERSILD & MUNCK
No. of pts .....	200	200	240	225	100	150	26	200
Preparation .....	S	P-A	P-A, P	P	P	P	P	P-P
Daily dose in I. U. ) × 1,000 for 6 days )		120-130	60-180	12-80 24-160	160-320	120-300	120-300	120-300
Inj. per day .....		3	3-6	8	8	2	1	1
Observation period in weeks .....	4	4	3	4-6	2-3	8	3	6
Weeks in hospital ....	4	4	2	4-6	1	2-4	3	1
Adenitis .....	29	0.5	3.3	2.2	1	2	11.6	1
Otitis media .....	4	0	0	0	3	1.3	0	1.5
Tonsillitis sec. ....	4	2	0	4.0		6.7	11.6	11.5
Rhinitis, purulent ....	9.5	2.5	0.4		1	0.7	7.7	2.5
Nephritis .....	1	0	0.4	0.4	1	0	0	0
Icterus .....	1	0					0	0
Secondary temp. > 38°					3	2.7		6
"      "      ≤ 38°						3.3		3
Scarlatinal reinfection.	1			0.9		1.3	3.9	1
Sinusitis .....	0.5	0	0	0.4	2	0	7.7	0
Total	48.0	5.0	4.1	7.9	8	12.0	42.5	17.5

Explanation of symbols: S = sulfanilamide, P = penicillin, P-A = penicillin-adrenalin, P-P = procaine penicillin.

Fig. 3. Complications in %.

tion; on a visit to his home it was learned that for a brief period he had had discharge from the ear, which now was dry. In none of the cases did mastoiditis develop.

Secondary tonsillitis appeared in 23 patients, 17 of whom were readmitted; in the remaining 6 cases the diagnosis was made anamnestically. In 14 cases growth of hemolytic streptococci was obtained in throat cultures. Twelve patients had hypertrophy of the tonsils.

The frequency of complications was somewhat higher under treatment with PP than under treatment with ordinary penicillin, but this difference was due entirely to the greater frequency of secondary tonsillitis. In this connection it is well to point out again that our patient material was under ambulatory control, so that undoubtedly some of the complications had nothing to

do with the original scarlet fever. Naturally, cases of secondary rhinitis are very difficult to estimate in a material under ambulatory control. We found 22 cases of purulent rhinitis lasting more than eight days. A great many of them were cases of ordinary "cold." It therefore seemed correct to reckon only those cases in which growth of hemolytic streptococci was found in nasal cultures. Even though the figure for these cases was too small, it probably was nearer the correct number than if we had reckoned all the cases.

One patient entered the hospital with hematuria and increased blood pressure, but subsequent urine analyses showed normal conditions. No instance of nephritis was observed.

A secondary rise in temperature — *i.e.*, a rise in temperature after the primary fall — without any demonstrable cause was observed in 18 cases, divided into two groups, with their respective maxima over and under 38°; the 6 cases in the latter group all appeared before the discontinuance of the treatment. Beyond these 6 cases, it was a characteristic feature that the temperature had a tendency to be “uncertain” towards the end of the treatment, though without a definitely rise. It may have been a form of drug fever, and probably 4 cases of the first group are to be interpreted in the same way.

The duration of the primary rise in temperature, reckoned from the first day of treatment, was on an average 1.6 days. For the distribution, see Fig. 4.

Temp. normal in 72 patients after < 1 day						
♂	♂	♂	47	♂	♂	1
♂	♂	♂	36	♂	♂	2 days
♂	♂	♂	15	♂	♂	3
♂	♂	♂	12	♂	♂	4
♂	♂	♂	5	♂	♂	5
♂	♂	♂	6	♂	♂	6
♂	♂	♂	6	♂	♂	7
♂	♂	♂	1 patient	♂	♂	14

Fig. 4. Return of temperature to normal under procaine penicillin treatment.

Two patients with scarlatinal reinfection in the fourth and fifth weeks, respectively, were readmitted to the hospital. In

one of these cases the cultures showed a change in the type of streptococcus; in the other case the streptococci were of undeterminable type ( $A_x$ ).

The variations in the antistreptolysin values (AST) and sedimentation rate (SR) are recorded in Fig. 5, where AST shows the slight rise usually found on treatment with ordinary penicillin (JERSILD (5, 6), STRØM (10)).

	On admission	7' day	4' week
AST .....	79	107	146
S. R. ....	27	14	10

Fig. 5. Average values for the antistreptolysin titer (AST) and sedimentation rate of red blood cells (S.R.).

### Summary

The material comprises 200 scarlatinal patients to whom procaine penicillin (PP) was administered intramuscularly for six days, the dosage being 120,000—300,000 I. U.  $\times$  1 daily. All the patients were under ambulatory follow-up observation for at least six weeks.

On admission 69.5 % of the patients showed a growth of hemolytic streptococci. After 24 hours' treatment with PP, hemolytic streptococci were found in only 3 % of the cases and upon discontinuance of the treatment in 1.5 %.

Thus the effect on the bacteriological status in scarlet fever as indicated by the outcome of the cultures is fully equal to the effect obtained with ordinary penicillin given twice a day.

The frequency of more serious complications is no higher for treatment with PP than for treatment with ordinary penicillin. No instance of nephritis or mastoiditis was seen in this material.

None of the patients presented any local or general by-effects from the treatment.

### Résumé

Le matériel comprend 200 cas de scarlatine traités à la pénicilline procaine (PP), 120 000—300 000 U. I. intramusculairement une fois par jour pendant six jours. Tous les sujets ont été soumis à

une observation de contrôle ambulante pendant un délai minimum de six semaines.

Lors de l'admission, 69,5 % des malades présentaient un développement de streptocoques hémolytiques. Après 24 heures de traitement à la PP, il n'a été constaté de streptococcie que dans 3 % des cas, et après la cessation du traitement que dans 1,5 %.

L'effet sur l'état bactériologique de la fièvre scarlatine, comme indiqué par le résultat des cultures, est donc entièrement égal à celui obtenu par la pénicilline ordinaire administrée deux fois par jour.

La fréquence de complications relativement graves n'est pas plus haute pour le traitement à la PP que pour celui à la pénicilline ordinaire. On n'a pas constaté de cas de néphrite ni de mastoïdite dans le matériel examiné.

Chez aucun des sujets il ne s'est présenté d'effets secondaires locaux ou généraux occasionnés par le traitement.

# Resumen

El material comprende doscientos casos de escarlatina tratados con penicilina procaina (PP), desde 120.000 a 300.000 U. I. inyectadas intramuscularmente una vez por día durante seis días. Todos los individuos han sido sometidos a una observación de control ambulatoria durante un tiempo mínimo de seis semanas.

En el momento de la admisión, el 69,5 % de los enfermos presentaba un desarrollo de estreptococos hemolíticos. Después de 24 horas de tratamiento a la PP no ha podido comprobarse estreptococcia más que en el 3 % de los casos, y después de terminar el tratamiento solamente en un 1,5 %.

El efecto sobre el estado bacteriológico de la fiebre escarlatina, como indicado por el resultado de los cultivos, es enteramente igual al obtenido por la penicilina ordinaria administrada dos veces al día.

La frecuencia de complicaciones relativamente graves no es más alta para el tratamiento a la PP que para el de la penicilina ordinaria. No se han podido comprobar casos de nefritis ni de mastoiditis en el material examinado.

En ninguno de los casos de los sujetos tratados se han presentado efectos derivados, locales o generales, ocasionados por el tratamiento.

### Zusammenfassung

Ein Material von 200 Scharlachpatienten wurde mit Procain-Penicillin (PP), 120 000—300 000 I.E. einmal täglich intramuskulär durch 6 Tage behandelt. Alle Patienten standen mindestens 6 Wochen unter ambulatorischer Nachkontrolle.

Bei Beginn ergaben 69,5 % der Patienten Wachstum von hämolytischen Streptokokken. Nach 24 Stunden Behandlung mit PP wurden nur in 3 % und nach Abschluss der Behandlung in 1,5 % der Fälle hämolytische Streptokokken gefunden.

Es ist der Effekt bei Scharlach sowohl in Bezug auf den bakteriologischen Befund als auch auf das Resultat der Kulturen vollständig gleich mit dem bei Behandlung mit gewöhnlichem Penicillin (2 mal täglich) erhaltenen.

Die Häufigkeit von ernsteren Komplikationen ist bei Behandlung mit PP nicht höher als bei der mit gewöhnlichem Penicillin. Es wurde bei diesem Material kein Auftreten von Nephritis oder Mastoiditis beobachtet.

Keiner der Patienten zeigte lokale oder generalisierte Nebenwirkungen der Behandlung.

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## **On Prenatal Changes in the Relative Weights of the Human Adrenals, the Thymus and the Thyroid Gland**

By

**ERIK EKHOLM and KALEVI NIEMINEVA**

Our knowledge of the factors influencing growth and development in fetal life is comparatively scanty. In the early phases of the embryonic period the so-called Spemann's organizers and other factors in firm combination with the germ cells determine the course of development. In the later period of growth the action of the hormones also plays an important part. The origin of these hormones is so far still a matter of dispute. According to some authorities the growth hormones originate either in the mother's organism, the placenta or the fetus. Possibly there is a question here of the general influence of the endocrinic secretions springing from different sources. The phase of the fetal period in which the hormonal influence comes to the fore is likewise a matter of controversy. In Switzerland, where this question has been much investigated in humans because of endemic goiter, they are of the opinion that the hormones rank first among the chemical substances affecting development (GUGGISBERG).

Up to now it has been difficult to determine by experimental research the quality and amount of secretion of the human endocrinic glands during fetal life. Anatomic investigation therefore forms a reliable foundation for appraising the function of the glandular cells. But in treating healthy and normal cases the relative size of the endocrinic gland is also of no little impor-

tance. In fact there are treatises on this topic to be found in the literature.

The earliest, most notable investigation in this line is JACKSON's work, based on American material. It comprises 43 fetuses varying in length from 6 mm to fullgrown. The material, however, is promiscuous, in that fresh cases are included along with fetuses long kept in fixative fluid.

In this work JACKSON examines the relative development of all the different parts of the body. As this is of importance in appraising the development of the endocrine glands, we shall recapitulate the main features.

1) The human ovum grows more than 10 000 times its size during the first fetal month, attaining a weight of 0.04 grams. The comparative increment in weight during the following months is shown by the multiples 74, 11, 1.75, 0.82, 0.67, 0.50, 0.47 and 0.45.

2) The head attains its relatively largest size in the second fetal month, when it is 45 % of the body weight, whereas at the moment of birth the weight of the head is 26 % of the body. The brains are likewise relatively heaviest in the second fetal month (20 %), decreasing evenly towards birth (13—14 %).

3) The trunk is relatively largest in the first fetal month, when it is 65 % of the whole weight, decreasing in the last fetal phase to 40—45 %. The extremities, on the other hand, grow in their relative size throughout the whole fetal period. At birth the upper limbs are 10 %, the lower 20 % of the body weight.

4) The heart is relatively largest during the first fetal month, when its weight is 5 % of the body's weight. Its relative weight then decreases rapidly up to the third fetal month, when it is 0.7 %, at which figure it remains till birth. The liver is at its largest during the second and third fetal months (7.5 %), whereafter its growth remains constant to the moment of birth (5—6 %). The size of the lungs is relatively greatest at the fourth fetal month (3.3 %), diminishing thereafter smoothly. At birth they are 2 % of the body weight. — The kidneys grow at first faster until the third fetal month, then more slowly, attaining their



maximum weight first in the seventh fetal month (1 % of the body weight). Thereupon their relative weight decreases a little only to increase again just before birth, when they comprise 1.05 % of the total weight of the body.

5) The thyroid gland and the thymus grow from the start quite regularly. Their relative weights at the moment of birth are on the average 0.3 % and 0.12 % respectively. The adrenals grow quickly in the beginning. They attain their relatively largest size in the third fetal month (0.45 %). Their size then decreases evenly, being at birth 0.24 %.

6) In the female fetus the internal organs are comparatively heavier, excepting the thymus, the lungs and the kidneys. — In the case of the organs forming pairs, the greater size of the right lung and of the left kidney and adrenal is notable even in early fetal life. In a mature fetus the internal organs with the exception of the thymus and the adrenals are heavier in alive-born child than in one born dead.

At the University of Minnesota, where JACKSON has been Director of the Department of Anatomy, they have made extensive investigations of growth development which in part at least are based on ample material. In connection with these investigations SCAMMON has examined specially the growth of the endocrine glands in the course of the embryonic and fetal periods. The results on the whole coincide with JACKSON's fundamental work.

The most recent publication on this topic which has come to our hands is the summary by CLATWORTHY and ANDERSSON based on the literature and illustrated by graphs showing the differential weights. It is founded chiefly on the works of JACKSON and SCAMMON. Their results agree, excluding some minor discrepancies, with the observations made above. It must be remarked that according to these writers, the adrenals attain their relatively greatest weight in the third fetal month, the thymus in the seventh and the kidneys in the seventh and eight fetal months.

In their work the French investigators LUCIEN and GEORGE direct their attention chiefly to the endocrine glands. They

have eliminated all material which does not conform to the general course of development. Of the quantity of their material there is no mention.

In their work they bring out relative weights, by which they mean the weight of the glands in relation to the weight of the whole body. Following up the relative weights gives a better opportunity of appraising the development of a single organ. As a good example of this might be mentioned the pituitary gland, which according to these writers grows continually from the beginning of the embryonic period to the end of life. Its relative weight, however, decreases constantly from the second fetal month on.

Their conclusions may be stated as follows. The pituitary gland attains its greatest value as early as the first and second fetal months, the adrenals in the fourth month and the thyroid gland in the fifth fetal month. The ratio between the weight of the thyroid gland and that of the fetus remains from this period on constant during the rest of the fetal period, whereas that of the pituitary gland and the adrenals decreases correspondingly. The investigators finally conclude that these results are not without some import in appraising the physiological function of the glands in question. The values given in their work will be more specifically presented along with our own material.

As to native investigators, taken in chronological order, this question has been treated by YLPPÖ, LEIDENIUS, UOTILA and HIILESMAA, but in general only in connection with their investigations of newborns.

YLPPÖ's material was gathered in Germany. On the basis of it he observed that in prematures the thyroid gland is relatively small, while enlarged thyroid is rare. — Likewise, the thymus is relatively small in prematures, especially if compared with fatty newborns.

LEIDENIUS examined the weight of the thyroid gland of healthy newborn male infants. The cases were collected at the Women's Clinic in Helsinki. For the thyroid gland she arrived at an average weight of 3 g. There was no notable difference in the average

weight of the thyroid glands of the boys whether they were born dead or alive. For the newborns who weighed less at birth, the average weight of the thyroid gland was greater than in heavier children of the same length class. The writer therefore considers, with reservations, this as proof that the thyroid gland of a fetus functions in the late fetal months.

In his investigations of the weight of the internal organs of Finns UOTILA also includes newborn infants. We shall return to his norm values in connection with our own observations.

On the basis of his investigations of material from South Finland HIILESMAA comes to the conclusion that goiter is quite common in newborns. The dissected and histologically examined cases however, were rather few. The normal weight of the thyroid gland for 16 newborn male infants he gives as 2.4 grams.

## **The Authors' Own Investigations**

### **The Material and Its Preparation**

In collecting fetal material for our histological work, we deemed it advisable to weigh some endocrine glands, inasmuch as in the literature we found only few investigations along these lines, and in the Scandinavian literature none at all. In the publications the autopsy data together with weight recordings were collected by different investigators over rather long periods of time. This circumstance, of course, only increased the possibilities of error.<sup>1</sup>

Our material has been collected during 1946—48 at the First, Second and Third Women's Clinics in Helsinki, where the parturients are chiefly from Uusimaa (Nyland). It covers 91 fetuses, ranging in weight from 24 to 2480 grams. All were normal; those which died during pregnancy or survived over 24 hours were excluded. We carried out the autopsies and the recording of the weights ourselves as soon as possible at the latest within 48 hours.

<sup>1</sup> Publication of our report was encouraged by C. E. RÄINHÄ, M. D.

In preparation of the organs the same method of procedure was naturally always followed, and because of the subsequent histological examinations great care was taken to obtain correct readings. Fat and loose areolar tissues were meticulously removed and from the kidneys the capsule was removed as well. In the case of the adrenals preparation was more difficult because they tear so easily and tend to hemorrhage. For the same reason we were not sufficiently successful even in the preparation of the other organs, so that we refrained from taking any values on them. Regrettably enough, we were not able to include the pituitary gland, as because of its situation preparation might well have damaged it too much for use in later investigations. The kidneys we took as comparative material, above all for the adrenals but also with a view to the other endocrinic glands, as their relative weight from the third fetal month remains practically constant (JACKSON).

The weighing was done by using scales with which the weight could be obtained, if requisite, with an accuracy of one milligram. We did all the weighing ourselves.

In our investigations we have also paid particular attention to the temporary changes in the weight of the endocrinic glands at the time of birth, as many writers, for instance NEUMANN and KOCH, have stressed the congestion in the region of the neck caused by birth. For this reason we used weight values taken at the Women's Clinic in Helsinki in 1926—1936 as a supplement to our own material. In handling this material we utilized the values as a separate group, inasmuch as the preparation and weighing were not homogeneous and not performed in the same way as by ourselves. After having ascertained that this material was almost identical with our own, we took from it weight values to our investigation of twins and malformations. Due differentiation was observed in the utilization of this material, it being denoted as Women's Clinic material, while that we dissected ourselves we called Own Material.

### Grouping of Fetuses by Weight

As a basis for classification of the fetuses we have used weight. The older fetuses were divided into *partus praematurus* (1250—2500 gr.) and *immaturus* (600—1249 gr.), the classification adopted by us (YLPPö). The small fetuses we divided somewhat arbitrarily by halving the lower limit of the heavier group, we took the resultant value as a new minimum limit. We have, moreover, been able to verify that according to the different sources (DELEE—GREENHILL, STOECKEL, STRATZ, YLPPö) the monthly development in weight during the fetal period just about corresponds to our groups. The corresponding weight classes and the fetal months are shown in the tables.

### Investigation of the Weights of the Glands

As in our material the largest fetus was about 100 times as heavy as the smallest, investigation of the weights of the endocrine glands as such could not give a correct picture of the part which the gland might have played in the development of the fetus in its various phases. A more correct idea could be formed by comparing the gland to the fetus as a whole; in this publication we designate this relation as the relative weight. We have directed our observations chiefly to the changes in the relative weights in the different classes. In the case of every fetus we calculated the relative weights of the organs in question. In the groups the average relative weight values were calculated per organ. The resultant values in the tables are presented by organs and illustrated by graphs.

We have calculated the intrinsic weights in the tables in such a way that the heaviest and the lightest were discarded, namely six values in each group, three of the heaviest and three of the lightest. In our opinion, the limit values thus arrived at correspond to reality better than if the mathematical average weight of the glands in each group were taken. The weight of the fetus as such doubles in each group.

### The Thyroid Gland

Determination of the normal size of the thyroid gland at various ages is rather difficult. According to most recent investigations for South Finland the maximum weight of a normal thyroid gland of a fully matured newborn is given as 5 g (HILLESMAA). His cases are from the same regions as those used in this work, so they are eligible for comparison in that respect. However, as above already stated opinions here differ as to the normal size (UOTILA: maximum 6 g) and as it is naturally still more difficult to determine the cases of goiter in fetus, we have discarded only plainly pathological cases.

For fetuses of the same weight and length we have found such extreme differences in the weight of the thyroid gland that one has been four times as heavy as another. The intrinsic weight of the gland increases throughout the whole embryonic and fetal periods, as is the case with all the glands under discussion (Table 1).

Table 1

Weight Class g	Fetal Month	Group A			Group B		JACKSON	LUCIEN and GEORGE
		n	p	p:P	n	p:P	p:P	p:P
Under 75	III	9	0.03-0.05	1:1623				1:9000
75-149	IV	12	0.08-0.15	1:947			1:1100	1:4000
150-299	V	17	0.15-0.28	1:925			1:1430	1:1500
300-599	VI	20	0.32-0.81	1:734	25	1:1140	1:1062	1:1300
600-1249	VII	14	0.95-1.9	1:646	34	1:903	1:775	1:1500
1250-2500	VIII-IX	16	1.65-3.18	1:671	35	1:711		1:1400

n: number of cases, Group A: own material, Group B: material of the Women's Clinic, P: weight of fetus body, p: weight of thyroid gland (g).

On examining the relative weights, one observes that the size of the thyroid gland increases evenly up to the partus immaturus stage from the ratio 1:1623 to 1:646, when the thyroid gland is at its greatest figure in relation to the body (Graph 1). In the partus praematurus group a diminution of the relative

weight is already perceptible, which tendency continues, according to UOTILA's values, in newborns. His values are 1:1129 for boys and 1:1002 for girls.

In comparing our own material with that of the Women's Clinic, we observe that the results are about the same in the partus praematurus group. The smaller values for the thyroid gland are to be noted in the two earlier weight classes in the Women's Clinic material.

The results of LUCIEN and GEORGE given for the sake of comparison are identical with our own as to the course of development. Nevertheless, it must be noted that the thyroid glands which they use as material are scarcely half the intrinsic weight of ours throughout. JACKSON's values are incomplete.

As mentioned in the introduction, it is most probable that the thyroid gland is on the average heavier in lighter fetuses of the same length class (LEIDENIUS, YLPPÖ). However, we have not been able to observe uniformity in this respect.

### The Thymus

The values for the weight of the thymus of fully-matured newborn fetuses vary greatly (HAMMAR, UOTILA, YLPPÖ).

At the same time however, we must emphasize that the weight of the gland is affected by the amount of fat tissues under

Table 2

Weight Class g	Fetal Month	Group A			Group B		JACKSON
		n	p	p : P	n	p : P	p : P
Under 75	III	11	0.03-0.045	1 : 1510			1 : 526
75- 149	IV	12	0.10-0.15	1 : 909			1 : 746
150- 299	V	18	0.15-0.4	1 : 806			1 : 671
300- 599	VI	20	0.45-1.22	1 : 488	26	1 : 602	1 : 571
600-1 249	VII	14	1.75-3.02	1 : 412	34	1 : 379	1 : 386
1 250-2 500	VIII-IX	16	3.8 -8.1	1 : 306	35	1 : 290	1 : 416

n: number of cases, Group A: own material, Group B: material of the Women's Clinic, P: weight of fetus body, p: weight of thymus (g).

the skin, which can also vary greatly in newborns. Still, the fact is not of any great moment in the material used in this investigation, as the fat tissues begin to grow more notably first in the last fetal month. For healthy adults HAMMAR considers the weight divergencies of the thymus fairly small in the same weight groups. Nonetheless, in our investigations we found that in fetuses of the same stage of development there were individuals in whom the divergence in the weight of the thymus was greater than in the thyroid gland. As example we may mention two 450 gram fetuses in whom the thymuses weighed 0.27 and 1.45 g and the thyroid glands 0.39 and 0.66 g, respectively. We could not observe any distinct correlation between the weights of the said endocrinic glands even in other respects.

In our material we observed that the relative weight of the thymus increases continually (Graph 1); its ratio of weight in the partus preamaturus group being 1:306. In the Women's Clinic material the growth tendency was the same and the relative values were of the same size class. — UOTILA's values were 1:387 for newborn boys and 1:392 for girls; consequently it seems that the thymus is at its largest just a little before birth.

JACKSON's results correspond on the whole with our own. The only difference is that in his work the gland appears to be at its largest at a slightly earlier stage. Nevertheless, it must be noted that his results in the first two weight classes are based on rather scanty material.

### The Adrenals

On account of their special course of development during embryonic and fetal life, the adrenals have long been an object of investigation. Their weight development has also been studied. According to the textbooks, in the embryonic period the gland is strikingly large in size. The total weight of both at the moment of birth is about 7 g, a weight which they regain only after some years.

The values in Table 3 are calculated for both adrenals together. In our own material the maximum relative weight is

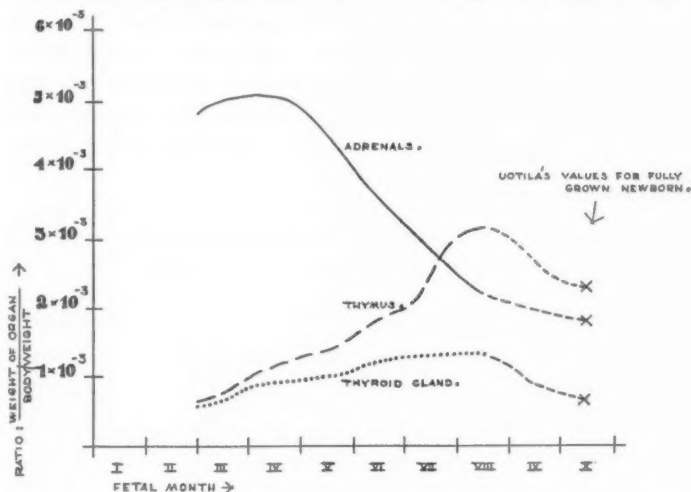


Table 3

Weight Class g	Fetal Month	Group A			Group B		JACKSON	LUCIEN and GEORGE
		n	p	p:P	n	p:P	p:P	p:P
Under 75	III	11	0.18-0.27	1:213			1:218	1:270
75-149	IV	12	0.53-0.68	1:191			1:270	1:150
150-299	V	18	0.83-1.28	1:192			1:278	1:300
300-599	VI	20	1.33-2.20	1:228	26	1:254	1:278	1:390
600-1249	VII	14	2.4-3.7	1:281	34	1:307	1:358	1:400
1250-2500	VIII-IX	16	3.5-4.78	1:394	35	1:417		1:430

n: number of cases, Group A: own material, Group B: material of the Women's Clinic, P: weight of fetus body, p: weight of adrenals (g).

in the weight class 75-149 grams, which corresponds to the fourth fetal month (Graph 1). The same observation can be made from the French material already mentioned. After the said period, the relative weight continually decreases, first slowly and then more quickly to the ratio of 1:394 in partus praematurus.



Graph 1. Development of the relative weights of the adrenals, the thymus, and the thyroid gland.

For newborns UOTILA gives the values 1:485 for boys and 1:471 for girls. It may be mentioned in this connection, in order to note the relatively large size of the adrenals during fetal life, that in an adult the ratio is 1:7000.

Upon examining the adrenals and the aforementioned endocrinic glands simultaneously, one observes that the former reach their maximum ratio in the embryonic period, whereas the others, on the contrary, do not attain their greatest values until the latter half of the fetal period. This is best shown by Graph 1.

On comparing the different endocrinic glands with one another, one observes that each separate one of them has its own individual course of development. It is only natural that behind this phenomenon there must be function.

### The Kidneys

In Table 4 the weight of both kidneys has been taken together. Like JACKSON, so we too can observe that the weight of the kidneys increase evenly, their weight in relation to the body as a whole remaining almost constant. In the literature it is stated that in early fetal life the adrenals are about the same size as the kidneys. In our material we have found three cases in weight group below 75 g in which the adrenals were as heavy or heavier than their respective kidneys. In the weight class 150—299 grams the adrenals were  $\frac{2}{3}$  the weight of the kidneys, whereas in partus praematurus they were only  $\frac{1}{4}$ .

Table 4

Weight Class g	Fetal Month	Group A			Group B		JACKSON
		n	p	p:P	n	p:P	p:P
Under 75	III	11	0.30-0.44	1:170			1:152
75-149	IV	12	0.72-0.95	1:134			1:123
150-299	V	18	1.21-2.03	1:134			1:112
300-599	VI	20	3.13-4.87	1:104	23	1:135	1:117
600-1249	VII	14	6.1-12.25	1:104	34	1:121	1:107
1250-2500	VIII-IX	14	13.6-19.25	1:101	35	1:122	1:130

n: number of cases, Group A: own material, Group B: material of the Women's Clinic, P: weight of fetus body, p: weight of kidneys (g).

### Differences in Weight between the Different Sexes

According to JACKSON the endocrinic glands and the internal organs in general are relatively heavier in girls than in boys, with the exception of the thymus, the kidneys and the lungs. On the strength of his material comprising 133 cases, the Swiss investigator NEUMANN is of the opinion that there is no difference in the thyroid gland. UOTILA's results for Finnish newborns show the same values as were obtained by JACKSON; to be sure, the differences in weight were in some cases very small, as for instance in the case of the adrenals and the thymus. It may be mentioned of the organs under discussion that according to UOTILA a full-grown man clearly has larger kidneys, whereas the other organs are of about the same weight.

Because of our scanty material, we have calculated the relative weight for the different sexes only in the weight classes 300—

Table 5

Weight	Boys		Girls		Boys		Girls	
	n	p:P	n	p:P	n	p:P	n	p:P
300-599 g	Kidneys				Adrenals			
A	10	1:106	8	1:102	10	1:219	8	1:231
B	11	1:131	11	1:141	11	1:264	11	1:216
1 250-2 500 g								
A	9	1:106	6	1:94	10	1:368	6	1:447
B	14	1:124	15	1:121	14	1:413	15	1:444
300-599 g	Thymus				Thyroid Gland			
A	10	1:536	8	1:429	10	1:799	8	1:653
B	11	1:579	11	1:602	11	1:1335	11	1:921
1 250-2 500 g								
A	10	1:350	6	1:253	10	1:815	6	1:518
B	14	1:313	15	1:283	14	1:815	15	1:621

n: number of cases, Group A: our own material, Group B: material of the Women's Clinic, P: weight of fetus body, p: weight of gland.

599 and 1250—2500 g. In the Table the organs forming pairs are given in their total weight ratio. Even in these weight classes the groups are small. On studying the table distinct differences can be ascribed only in the case of the thyroid gland, and there specially in the partus praematurus class. On the strength of this amount of material it is difficult on the whole to draw any conclusions, but it can be presumed that the relatively greater weight of the thyroid gland is attributable to the smaller birth weight of the girl infants.

### The Organs forming Pairs

The mutual relations in the sizes of the organs forming pairs are interesting only from the standpoint of anatomy. On this account we have not calculated average values for these, but only examined which half of each organ was the larger or whether they were equal in size.

In our material the left kidney was larger in 47.8 % of the cases and the right in 38.3 %, while in the rest both were equally large. In our opinion one cannot speak of the human left kidney

Table 6

Weight Class  g	Kidneys						Adrenals					
	A			B			A			B		
	+	=	-	+	=	-	+	=	-	+	=	-
Under 75	3	4	4				2	3	6			
75- 149	6	1	5				5	1	6			
150- 299	2	3	13				8	1	9			
300- 599	8	2	10	8	7	8	9	1	10	5	4	17
600-1 249	4	2	8	14	3	17	5	2	7	11	7	16
1 250-2 500	9	—	6	28	9	30	7	3	6	6	5	56
Total	32	12	46	50	19	55	36	11	44	22	16	89
A + B	82			31			101			58		
							27			133		

A: own material, B: material of the Women's Clinic. +: right half larger, =: both halves equal in size, -: left half larger.

as being clearly of larger size than the right. As to the adrenals, however, the left was larger in 61.1 % of the cases and the right in 26.6 %. Even on the strength of this material, the results appear to favour the left adrenal as being the larger in size.

### The Endocrinic Glands of Twins

In the literature we have found no special mention of results obtained in autopsies of fetal twins. Since we feel that because of the different conditions of development of the twins, these investigations may bring further light into the possible function of the endocrinic glands during the fetal period, we have treated separately all normal twin cases in order to observe in them the mother's influence.

On comparing the resultant values with the normal values of fetuses of the same weight and each element of a pair with the other, one can draw conclusions as to the functional correlation of the endocrinic glands between the mother and the fetus. If the mother's hormonal influence on the growth of the endocrinic gland is predominant, it is most probable that the glands of the twins will be of the same relative size class. On the other hand, if the glands of the fetus function independently and are dominated by the conditions prevalent in the fetus, it naturally follows

Table 7

Weight Class g	n	p:P	p:P
		Both Kidneys	Both Adrenals
600-1 249	21*	1:131	1:420
1 250-2 500	20	1:131	1:485
		Thymus	Thyroid gland
600-1 249	21*	1:454	1:986
1 250-1 500	20	1:382	1:560

n: number of cases, p: weight of gland, P: weight of fetus body. \* Odd number results from the fact that amongst the twins one triplet was included.

that the endocrinic glands in the pair of twins will in many instances be of distinctly different sizes.

Upon comparing the resultant relative weight averages of the organs of the twins first to respective values for normal material, we ascertain that there is no distinct difference between them. On the other hand when we compared the relative weights of the endocrinic glands of the twin halves among themselves, our attention was drawn to the fact that in the relative weights of the twin pairs there were not so great differences as in the normal material collected by us. As an example we may mention the adrenal values in the *partus praematurus* group expressed in percentage of the total body weight by twin pairs: 0.22 and 0.26; 0.33 and 0.23; 0.19 and 0.16; 0.27 and 0.20; 0.24 and 0.24; 0.12 and 0.12; 0.18 and 0.15; 0.20 and 0.21; 0.19 and 0.20; 0.26 and 0.20.

Despite the scantiness of the material, the above results in our opinion give us reason to conclude that alongside of inherited characteristics there are factors influencing the weight development of the endocrinic glands of the fetus which spring from sources outside the fetus.

Moreover, we were able to ascertain that in eighteen of the twenty pairs of twins the weights of the thyroid and the thymus were greater with the same twin.

#### **The Effects of Labour on the Weight of the Endocrinic Glands**

Many investigators have observed the changes which parturition itself causes in the child's organs, especially the great sensitiveness of the endocrinic glands. KOCH and NEUMANN in their research noted that after birth the thyroid gland is very congested but that this congestion disappears in the case of a live child in as little as one—three days. NEUMANN emphasized the great importance in this respect of some pathological parturitions such as face presentation. On the strength of his investigations HILLESMAA considered that even factors others than the mechanism of birth had their influence. He arrived at his hypothesis in investigating cases of caesarian section.

We have given due consideration to this fact in order to observe how great these changes in weight are. In addition to the normal partus praematurus material of the Women's Clinic, which, as was mentioned early in this work, included only individuals who were born dead or died within the first 24 hours, we also, in order to clarify the above fact, took as comparative material children who survived two—five days where the autopsy revealed the cause of death to be purely prematurity.

Table 8  
Weight Class 1 250–2 500 g

Organ	Died at Birth or Within 24 Hours		Died Within 2–5 Days	
	n	p : P	n	p : P
Thymus.....	35	1 : 290	32	1 : 445
Thyroid Gland.....	35	1 : 711	32	1 : 894
Both Kidneys .....	35	1 : 122	32	1 : 151
Both Adrenals.....	35	1 : 417	32	1 : 465

n: number of cases, p: weight of organ, P: weight of body.

From the table we see that in each case there was a decrease in the organs weighed. Nevertheless, it must be observed that the thymus and the thyroid gland decreased more notably than the others. The loss in weight of the thymus was an ample one third. It is possible that there were other contributory factors besides the simple disappearance of congestion, perhaps an inflammation not observed in the autopsy. In our opinion the comparison shows that in a work like this the extraordinary blood-richness of the organs must be taken into account.

#### The Weight of the Endocrinic Glands in the Malformed Fetus

Upon dissecting anencephalous fetuses we could observe that their adrenals were regularly smaller than normally, which fact BERGSTRAND mentions as characteristic of them. From autopsies

on the material from the Women's Clinic we found in partus praematurus and partus immaturus groups 9 anencephalous cases, the glands of which were weighed. The adrenals of each was at most half the size of those of normal material. The relative average weight of the adrenals for the anencephalous malformed fetuses was 1:1535, whereas the corresponding normal values in the groups mentioned were 1:307 and 1:417. Concerning the other glands it might be mentioned that the thyroid glands vary widely in size in both directions when compared with normal data, only the thymus being on the whole of normal size.

These pathological changes in the endocrinic glands were not, however, found to appear uniformly in spina bifida and hydrocephalous malformations.

### Summary

The authors examined the weight during the fetal period of the adrenals, the thymus, the thyroid gland and for purposes of comparison the kidneys of fetuses up to 2500 grams and observed the following.

The adrenals were relatively largest at the fourth fetal month and the thyroid gland at the partus immaturus stage, whereas the thymus increased steadily. There was distinct diminution of weight after labour, greatest in the case of the thymus.

The weight of the endocrinic glands of the different sexes, of twins and of each half of a pair organ was examined. The glands in anencephalous, spina bifida and hydrocephalous cases were also weighed.

The authors consider that the variations in the weight development of the different endocrinic glands can no doubt be ascribed to their function during the fetal period.

### Résumé

Les auteurs ont examiné le poids, pendant la période foetale, des glandes surrénales, du thymus, de la glande thyroïde et, pour comparaison, des reins de fœtus pesant jusqu'à 2 500 grammes. Ils ont observé ce qui suit:



Les glandes surrénales étaient relativement le plus grandes au quatrième mois de gestation, la glande thyroïde l'était au stade de l'accouchement prématuré, tandis que le thymus croissait constamment. Il y avait une diminution de poids marquée après l'accouchement, qui était le plus forte en ce qui concerne le thymus.

On a examiné le poids des glandes endocrines des deux sexes, de jumeaux et celui de chaque moitié d'un organe formant paire. Les glandes de cas d'anencéphalie, de spina bifida et d'hydrocéphalie ont aussi été pesées.

Les auteurs estiment que les variations du développement du poids des différentes glandes endocrines peuvent sans doute être attribuées à leur fonction pendant la période foetale.

### **Zusammenfassung**

Die Autoren untersuchten das Gewicht der Nebennieren, der Thymus, der Thyreoidea in der fötalen Periode und zum Vergleich das der Nieren bei Fötus bis zu 2 500 gr und beobachteten Folgendes:

Die Nebennieren waren relativ am leichtesten im 4. Fötalmonat, die Thyreoidea bei den Frühgeburten gleich, während die Thymus ständig zunahm. Es wurde eine Gewichtsabnahme nach Arbeit festgestellt, am grössten bei der Thymus.

Es wurde das Gewicht der endokrinen Drüsen bei beiden Geschlechtern. bei Zwillingen, bei einer Hälfte sowie bei den Organpaaren untersucht. Auch die Drüsen bei Fällen von Anenzephalus, Spina bifida und Hydrozephalus wurden untersucht.

Die Autoren nehmen an, dass die Unterschiede der Gewichtsentwicklung der verschiedenen endokrinen Drüsen ohne Zweifel deren Funktion während der fötalen Periode zugeschrieben werden können.

### **Resumen**

Los autores han examinado el peso, durante el período fetal, de las glándulas suprarrenales, del timo, de la glándula tiroide y, por comparación, de los riñones de fetos con un peso hasta 2 500 gramos. Han observado lo siguiente:

Las glándulas suprarrenales eran relativamente las mayores en el cuarto mes de gestación, la glándula tiroide lo era en el estado de parto prematuro, mientras que el timo crecía constantemente. Había una marcada disminución de peso después del parto, siendo la más fuerte la del timo.

Se ha examinado el peso de las glándulas endocrinas en los dos sexos, de gemelos y de cada mitad de un órgano formando par. Las glándulas de los casos de anacefalia, de spina bífida y de hidrocefalia se han pesado también.

Los autores estiman que las variaciones en el desarrollo del peso de las diferentes glándulas endocrinas pueden ser atribuidas, sin duda, a su función durante el período fetal.

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## **On the Ability of Enuretic Children to Hold Urine**

by

**NIILO HALLMAN**

The most common causes of enuresis continuing after the third year of life are considered to be, in addition to some psychogenetic factors, lack of training and a so-called irritable bladder, (MITCHELL-NELSON) showing an exaggerated susceptibility to certain irritants. On the other hand, organic defects in the bladder itself are extremely rare (AMBERG, STOCKWELL & SMITH). Nor have deviations from the normal been found in the absolute volume of the bladder. In order to ascertain the functional volume of the bladder, I have performed a number of tests to determine the ability of enuretics to hold urine and compared the results with those obtained from normal children of the same age.

### **Method of Research**

Sixty three enuretics from 3 to 13 years of age of whom 45 were boys and 18 girls, were examined. A careful clinical examination revealed no external defect or infection of the urinary passages in any of these children. Cystoscopy, however, was not performed. Manifestly imbecile or neurologic cases and children suffering from endocrine diseases were not included. The research was not concerned with the psychic basis of the disease or any other possible etiology.

The control series consisted of 129 children, of whom 81 were boys and 48 girls, treated at the Clinic for some other disease.

The functioning of the bladder of each enuretic was tested some

days after admission to the Clinic, when the patient had already had the opportunity to become accustomed to his new environment, by measuring the volume of urine at different times of miction for two days. After this, the patient was given a drink of 500—1 000 cc of water or juice, the quantity depending on his size, subsequent to which attempts were made, by diverting his attention to other things and even by exercising will power, to get him to retain his urine for as long a time as possible, after which the amount of urine was registered again over a period of four—six hours.

The method of research applied to the control children was identical. However, the quantity of urine before administering water was not registered. In the evening, after making these children drink a corresponding amount of water, 0.1—0.3 Medinal was also given immediately before bedtime, and the amount of urine was measured on awakening.

### Results

The maximal functional volume of the bladder in individual children is illustrated by the following Figures (1, 2, 3). The variations are considerable even in children of the same age. Apart from a few exceptions, the functional volume of the bladder was a minimum of 300 cc as early as the age of 4 in children of both sexes and frequently considerably more, up to double this amount. As the child grows older, the capability to hold urine naturally also increases. No difference between the sexes was found. Generally the maximum quantities of urine were approximately of the same volume in the morning during active holding and on awakening before midnight. Small variations appeared in either direction, however.

In the majority of enuretics the volume contained was below 300 cc, even up to the age of 9 years. Of 43 patients only 13 had this volume or more. In other children only 4 of 25 could hold a volume of 550 or more, while in normal children of the same age the volume fell short of this amount only in a few exceptional cases. It follows that a relatively distinct difference could be

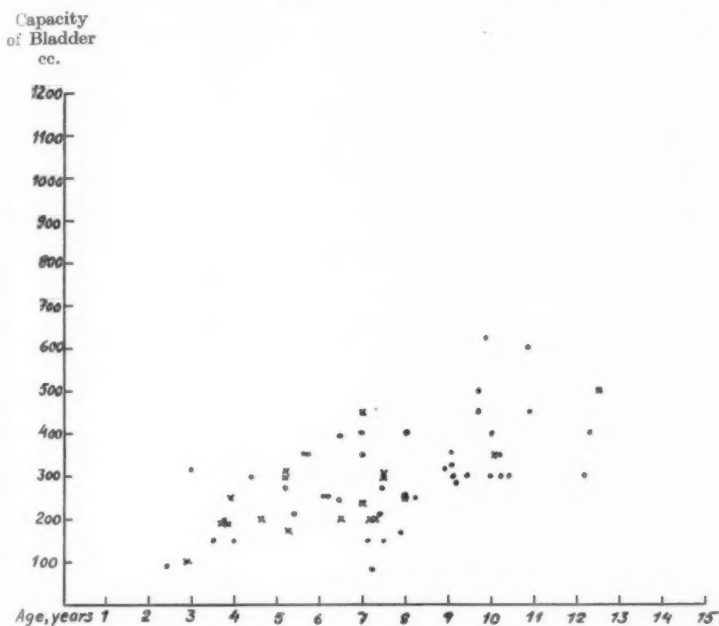


Chart 1. Functional Capacity of Bladder in Enuresis Nocturna.

• boys.  
 × girls.

ascertained as compared with the functional volume of normal children.

After drinking water, the highest amount of urine was found in normal children without exception as early as in the following miction. For  $\frac{1}{3}$  of the enuretics, however, the amount of urine obtained in the first specimen after drinking was not the largest. The maximum was not achieved until the next time, when the patient in question appeared to be absorbed in other occupations and had forgotten all about urination. In some cases an equally high maximal holding was not obtained in connection with the drinking of water as had been attained on previous days when registering normal volumes of urine.

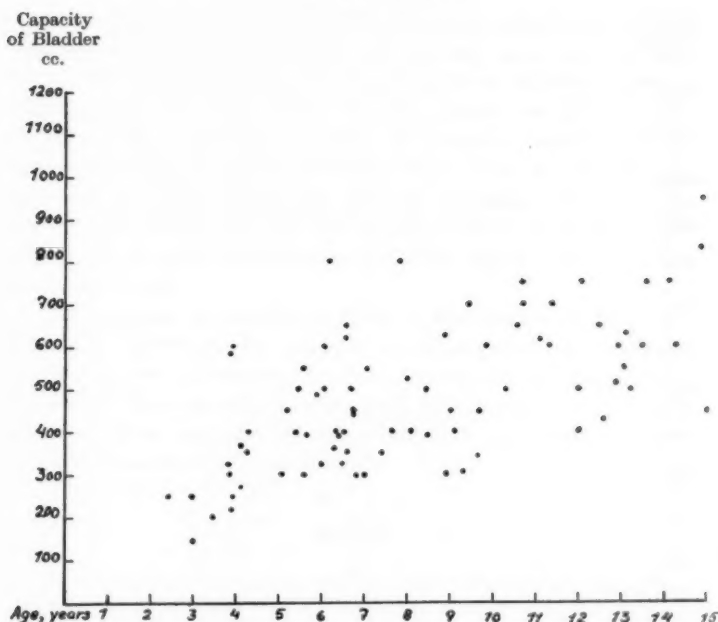


Chart 2. Functional Capacity of Bladder in Normal Boys.

### Comment

→ The above tests regarding the customary holding of urine show that enuretics generally appear to have a smaller functional bladder capacity than normal children. If we consider the normal amount of urine, i. e. 600—700 cc at the age of 3 to 5, 650—1 000 at 5—8 and for those 8 to 14 800—1 400 cc/24 hours (MITCHELL-NELSON), it is possible that at least in some cases the functional volume is insufficient to contain the whole quantity of urine accumulating in the bladder at night and varying from  $\frac{1}{5}$ — $\frac{1}{4}$  of the amount passed daily. If the sensation produced by the filling of the bladder is not sufficiently strong to cause awakening, bed-wetting takes place. Whether this is due to lack of training, depth of sleep, dreaming or to the fact that so-called bathyesthesia is

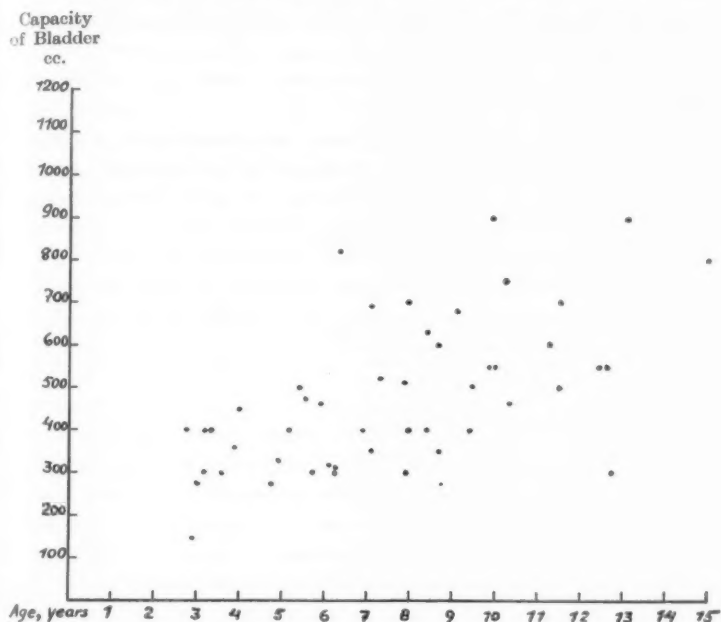


Chart 3. Functional Capacity of Bladder in Normal Girls.

generally weaker in enuretics than in healthy individuals is another matter (EDERER and LEDERER). At any rate, by training and especially by planned awakenings during the night (for instance, PFAUNDLER and MOROWER and MOROWER) satisfactory results have been achieved.

It is possible that the small functional bladder volumes found by me are due to psychic factors and are perhaps, at least in some cases, the consequence and not the cause of enuresis. Upbringing and training may have been neglected in the beginning. Later on, urination and enuresis have become an every-day topic at home and have led to the hospital after rewards and punishments. Possibly the fear of wetting has made the whole urination reflex more delicate. In the treatment of enuretics it is necessary to keep

even this possibility in mind and not expect too much from the child at the beginning.

### Summary

The functional bladder capacity has been tested in 63 enuretics (45 boys and 18 girls) by endeavouring to get the children to hold their urine as long as possible. Among the cases there were no organic diseases, infections of the urinary passages, cases of debility or patients suffering from endocrine diseases. Compared with the control material (81 boys and 48 girls) the capacity of the bladder was generally lower in the enuretics, apart from a few exceptions.

### Résumé

La capacité fonctionnelle de la vessie a été examinée chez 63 enfants atteints d'énurésie (45 garçons et 18 fillettes) en s'efforçant d'obtenir des enfants qu'ils retiennent leur urine aussi longtemps que possible. Parmi les cas il n'y avait pas de maladies organiques, d'infections des voies urinaires, d'enfants faibles, ou souffrant de maladies endocriniennes. Comparée au matériel de contrôle (81 garçons et 48 fillettes) la capacité de la vessie était généralement plus faible chez ceux atteints d'énurésie, à part quelques rares exceptions.

### Zusammenfassung

Die funktionelle Kapazität der Blase wurde bei 63 Bettnässern (45 Knaben und 18 Mädchen) untersucht. Die Kinder sollten den Urin so lange wie möglich einhalten. Unter diesen Fällen wurden organische Krankheiten, Infektionen der Urinwege, Debile- oder Patienten mit endokrinen Erkrankungen ausgeschlossen. Im Vergleich mit dem Kontrollmaterial (81 Knaben und 48 Mädchen) war die Kapazität der Blase, abgesehen von wenigen Ausnahmen, bei den Bettnässern geringer.

### Resumen

La capacidad funcional de la vejiga ha sido examinada en 63 enuréticos (45 muchachos y 18 muchachas) ensayando hacer



retener a los niños su orina el mayor tiempo posible. Entre los casos no había defectos orgánicos, infecciones de las vías urinarias ni débiles o pacientes sufriendo enfermedades endocrinas. Comparado el material de examen (81 muchachos y 48 muchachas) el resultado ha probado que la capacidad de la vejiga era generalmente más baja en los enuréticos, aparte de algunas raras excepciones.

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## **On the Use of Hyaluronidase on Hypodermoclysis in Infants**

by

**NIILO HALLMAN, EINO KULONEN and OLOF FORSANDER**

Recent theoretical research work has paid particular attention to the polysaccharides of the connective tissue, among which the hyaluronic acid, forming the main part of the medium's gelatinous substance, has been especially studied. This research work was initiated following the observation made in 1928 (Duran-Reynals) that testicular extract is capable of promoting the permeability of the dermal connective tissue. The actual cause of the phenomenon remained obscure for a decade, until CHAIN and DUTHIE demonstrated, in 1939, that it was due to an enzymic effect on an already known polysaccharide also appearing in the skin, the hyaluronic acid. Hyaluronidase, the enzyme involved, was afterwards found not only in the testicles, but also in several bacteria as well as animal poisons, and the theory was advanced that nature meant to promote in this way the spreading of toxins in the connective tissue.

No attempts were made to apply the phenomenon described above in practical medicine until quite recently, when references to tests performed began to appear simultaneously in different places. This is probably to be attributed to the difficulties in manufacturing the preparations. The nature of the phenomenon is such that it involves merely local and auxiliary therapy; hence it was at first unable to arouse any special interest in general medical circles, all the more so since the application of remedies does not cause difficulties. It is a different matter as far as pe-

diatries are concerned; in this field particularly since the significance of the fluid parenteral treatment was realized, practical difficulties began to arise in the routine work, often threatening to endanger the success of the therapy. Repeated intravenous infusions are not always possible, particularly in diarrhea and post operative states, and a preparation of the vein cannot be recurred to always and under any circumstances. One is compelled to use subcutaneous infusions. These are, however, often attended by difficulties of absorption, most annoying particularly in those cases where, due to circulatory disorders, the loss of fluid must be compensated by more urgent measures.

Previously testicular preparations were used (HECHTER and DOPKEEN 1946, HENDERSON, KING 1948, SCHWARTZMAN 1949, BURKET and GYÖRGY 1949) which could also be obtained commercially. The high price due to a complicated process manufacture was, however, a drawback. Extensive purification is imperative in order to prevent allergic reactions, particularly if these preparations have to be used for any length of time. In addition, penetration of the connective tissue does not form part of the physiological function of the testicular enzyme, as is the case where bacterial enzymes are concerned.

Owing to the short supply, we came to test bacterial hyaluronidase remedies of our own preparation, and these experiments gave us the opportunity to compare them with testicular preparations.

### Preparations Used

The testicular preparation was manufactured by Treemods and Co. and claimed to contain 100 TRU/mg.

The bacterial preparation was made as follows: fluid containing hyaluronic acid was taken from the umbilical cord and added to the Gladstone-Fielde culture medium in order to stimulate the enzyme formation, and a streptococcal strain (Group A, Type 4, Strain H 713) producing hyaluronidase was introduced).<sup>1</sup>

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<sup>1</sup> The strain was originally obtained from Dr H. J. ROGERS, to whom we are greatly indebted.

After 24 hours growth the culture was centrifuged until it became clear and fractioned with ammonium sulfate, preserving the precipitate between  $\frac{1}{3}$  and  $\frac{2}{3}$  of the saturation; this was subjected to additional purification by performing its absorption to colloidal ferrihydroxide at a pH of 5.6 and elution with sodium carbonate (Rogers 1948) was carried out twice. Finally dialysis with glycerine was performed and a solution obtained which was suitable for storage and contained 0.26 mg/ml nitrogen and about 2 500 TRU/mg.

### Research Methods

The effect of hyaluronidase was studied on 32 patients aged from 1 month to 2 years, who were mainly convalescent after intestinal infection. Twenty six of them were given fluid 20 to 40 cc subcutaneously simultaneously in both flanks, with hyaluronidase added to one of the injections. Instead of the one-time injection 8 patients were administered 150 to 250 cc fluid by the same method, and it was allowed to drip without producing any greater tension. As infusion fluid, a solution of sodium chloride, isotonic glucose or a mixture of both was used. The node thus produced was examined every fifth minute by palpating with the hand. It was often difficult to assess the final stage, but the difference between one side and the other was easy to establish.

Crystalline hyaluronidase was weighed and dissolved in water immediately prior to injection. The bacterial enzyme was diluted with sodium chloride to 1:40 before injecting and the necessary quantity taken afterwards. 1 ml of this dilution corresponds to approximately 1 mg of the enzyme.

### Results

As illustrated by the tables appended to this paper, the absorption was unmistakably more rapid when hyaluronidase was administered simultaneously, both in those cases (Table 1) where the fluid was introduced as a single subcutaneous dose, and in those where a drip infusion was used. (Table 2.) In 3 cases the difference was uncertain however. Two of them exhibited gross

Table 1.

Case	Age Months	Clinical Diagnosis	Fluid used		Hyal- uroni- dase mg	Resorp- tion Time Min.		Remarks
			ml	Qual- ity		H	W	
S. T.	3	Conv. p. gastroent.	40	S.	0.5	65	182	T. fever 38.7
A. P.	17	"	"	"	0.75	65	260	" "
Y. L.	1	"	20	"	0.75	51	139	" "
A. P.	"	"	30	"	0.5	108	213	" fever 39.0
J. S.	1 1/2	"	40	"	0.5	108	358	" fever 38.7
B. T.	6	"	20	G.	0.5	30	183	B "
A. V.	5	Dystrophia	"	"	0.5	47	170	" "
M. J.	30	Coelicia	"	"	0.5	25	177	" "
A. T.	4	Nihil. obj.	"	"	0.5	—	—	" impossible to judge
H. L.	4	Conv. p. gastroent. ac.	"	"	0.5	60	175	" "
A. P.	4	" [oedema	"	"	0.5	121	285	" "
K. K.	3	Gastroent. ac. oedema	"	"	0.5	—	—	" "
S. V.	3	"	"	"	0.5	153	193	" "
E. K.	6	Gastroent. ac.	"	"	0.5	163	257	" "
O. S.	2	Conv. p. gastroent. ac.	"	S.	1.0	127	185	" local redness
P. S.	2	"	"	"	1.0	71	160	" "
H. L.	4 1/2	"	"	"	1.0	33	95	" "
M. R.	7	"	"	"	1.0	80	272	" "
E. H.	2 1/2	"	"	"	1.0	85	290	" "
S. V.	3 1/2	"	"	"	1.0	165	245	" "
E. A.	2	"	"	"	1.0	45	200	" "
L. B.	2 1/2	"	"	"	1.0	117	192	" "
L. P.	24	"	"	"	1.0	83	238	" "
O.	1	"	"	"	1.0	95	267	" "
A. H.	2	"	"	"	1.0	98	188	" "
O. P.	2	"	"	"	1.0	55	207	" "

S. = Saline

W = without hyaluronidase

G. = 5 % Glucose

T = testicular

H = with hyaluronidase

B = bacterial preparation

edema at the time of carrying out the test, and in one it was difficult to assess the result owing to a thick layer of fat. It is noteworthy that in 2 other edematous patients a greater rate of absorption was clearly revealed after the administration of the enzyme. In these exceptional cases it could be clearly seen that

Table 2.

Case	Age Months	Clinical Diagnosis	Fluid used		Hyal- uroni- dase mg	Dutation of Drop		Resorp- tion Time Min.		Remarks
			ml	Qual- ity		H.	W	H	W	
A. P.	3	Conv. p. gastroent.	150	G.	1.0	125	135	330	660	T
S. T.	2	"	150	"	"	160	210	550	400	T oedema
K. V.	6	"	250	"	"	145	265	735	870	B
L. H.	1	"	"	"	"	185	555	845	1 710	"
N. V.	4	"	"	"	"	295	295	975	1 625	"
O. P.	7	"	"	"	"	160	585	495	1 365	"
M. R.	5	"	"	"	"	398	520	760	1 830	"
K. K.	2	"	"	"	"	120	360	675	1 770	"

S, G, H, W, T, B = see table 1.

the tension was reduced on the side where the enzyme had been applied, only two minutes after the injection. The node was soft and appeared to be spreading over a more extensive surface.

In 4 cases a flush could be seen for some hours on the side where hyaluronidase had been introduced, but it invariably receded without leaving any reaction. The relatively impure testicular preparation induced in 3 of 5 cases a rise in temperature to 39° C. Within 12 hours, however, the temperature returned to normal in these instances as well. No deterioration whatever in the general condition could be observed in connection with any of the infusions. The rate of resorption was approximately the same with both these preparations. On the other hand, the glycerine preparation derived from bacteria failed to produce a rise in temperature in any single instance.

It should be said, moreover, that hyaluronidase was used in 5 cases in severely toxic infants with acidosis to whom it was impossible to administer the fluid intravenously without previous preparation of the vein. In all of them the fluid was rapidly absorbed and their conditions improved greatly so that therapy could be continued using the i. v. technique.

With the aim of studying the effect of hyaluronidase on the

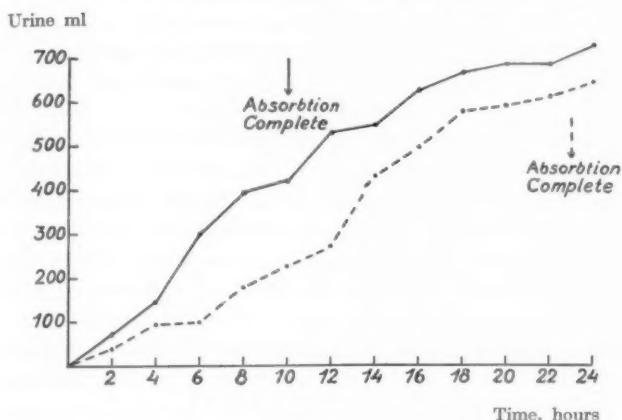


Fig. 1.

amount of urine, 5 patients were administered a subcutaneous drip infusion of 250 cc on successive days under exactly identical conditions. One day hyaluronidase was used, and on the second day the infusion into the other side was made without it. The times of miction and quantities of urine were registered. As illustrated by the typical example in Fig. 1, the volume of urine during the hours after infusion was considerably larger where the enzyme had been administered, which is due in the first place to a rapid mobilisation of the fluid introduced into the organism.

### Discussion

According to SCHWARTZMAN (1948), the rate of absorption can increase up to 14 times under the influence of hyaluronidase. In our test the difference was two to five times both in testicular and bacterial preparations, but as already mentioned, quantitative estimation is difficult. At all events, the resorption had improved and not a single instance where the bacterial preparation had been used revealed any undesirable effects. The cost of this remedy is considerably less than that of the testicular preparation, a circumstance, which is naturally likely to facilitate its use.

In some instances where edematous infants were concerned we were unable to observe any noteworthy difference with the use of hyaluronidase. This seemed fully natural and consistent with Schwartzman's earlier observations.

The effect is purely local and as regards contraindications, it is advisable to bear in mind that one should not unnecessarily disturb the physiological function of the tissular polysaccharides in filling the interspace between the connective tissues and preventing penetration of deleterious substances as well. Under these circumstances, local infection especially must be considered a contraindication.

There are also references in the literature (BURKET and GYÖRGYI 1949) which indicate that in excretory urography, hyaluronidase might be applied with good results, as it would eliminate the necessity of introducing any opaque medium into the vein and the excretion would still be fairly efficacious without negative collateral effects. Our tests with the excretion of urine suggest that a certain benefit might be expected in this connection, a circumstance, which would increase the practical adaptability of the study referred to. The same possibilities are also present in the use of local anesthesia, where it has been established that novocaine can be made to spread with much greater facility and the desired result can be achieved with considerably smaller amounts.

No study has yet been made of the possibilities of applying hyaluronidase in the treatment of certain skin diseases but presumably it would enable remedies to penetrate more easily into the skin.

### Summary

The writers studied the effect of testicular and bacterial hyaluronidase on the resorption of fluids introduced subcutaneously, as well as their influence on the excretion of urine. The bacterial preparation, which is much cheaper, was found to be as efficacious as and with fewer untoward effects than the impure testicular preparation. The rate of urinary excretion rose considerably.



### Résumé

Les auteurs ont étudié l'efficacité des hyaluronidases de testicules et bactériens sur la résorption des fluides introduits par injections sous-cutanées, ainsi que leur influence sur l'excrétion de l'urine. On a constaté que le produit bactérien, qui revient bien moins cher, est aussi efficace et a moins d'effets secondaires fâcheux que le produit impur des testicules. La rapidité de l'excrétion est considérablement accélérée.

### Zusammenfassung

Die Autoren haben die Wirkung von testikulärer und bakterieller Hyaluronidase bei der Resorption von subkutan zugeführten Flüssigkeiten, sowie den Einfluss auf die Urinausscheidung untersucht. Das bakterielle Präparat, welches billiger ist, erwies den gleichen Effekt und verursachte weniger unangenehme Beiwirkungen als das unreine testikuläre Präparat. Die Geschwindigkeit der Urinausscheidung stieg beträchtlich.

### Resumen

Los autores han estudiado el efecto de hialuronidazas testiculares y bactericas sobre la resorción de líquidos inyectados por vía subcutánea, así como su influencia sobre la excreción de orina. Se ha comprobado que la preparación bacterica, que es mucho menos cara, es también eficaz y causa menos efectos desfavorables que la preparación testicular impura. La rapidez de la excreción de orina ha aumentado considerablemente.

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## **Premature Infants in a Swedish County Hospital: Frequency and Early Prognosis**

By

**KJELL L. MÖLLER**

### **Introduction**

A clearer conception of the prognosis of the premature infant in various places would be of interest and also of practical value for comparative studies of the relative efficacy of the therapeutic measures adopted in various hospitals. Unfortunately, earlier publications do not as a rule lend themselves to comparison. This is due mainly to the use of different criteria in the classification of premature births, live-births and still-births, as well as to the varying selection and composition of the different series of cases. The *actual* prognosis, i.e. the total number of lost infants due to prematurity, is still more or less unknown.

### **Material**

The records of prematures at Borås Hospital, which has separate obstetric and pediatric departments, were considered suitable for an investigation for two reasons: 1) the area from which patients are admitted is relatively large, and 2) the respective chiefs of these two departments were the same throughout the entire period covered by the investigation, for which reason it seems feasible to assume a uniform evaluation of the indications and interpretation of clinical symptoms and signs.

Those infants who after parturition "breathed and showed signs of life" and weighed  $> 600 - \leq 2\,500$  g were, in accordance with YLPPÖ's suggestion, classed as premature live-births. Those still-born infants weighing  $\leq 2\,500$  g and with a body length of

$\geq 35$  cm were classed as premature still-births (this lower limit of distinguishing premature still-births from abortions had to be used because the weights of fetuses below that length have not been recorded).

The series includes *all* infants fulfilling the above conditions who were born at the Maternity Dep't of Borås Hospital during the years 1939—1948. The material was collected by the author, who himself perused all the records from this period of the Maternity Dep't and when necessary the Pediatric Dep't.

### Census

The following statistical information taken from "Redogörelser rörande hälso- och sjukvården i Älvsborgs län" for the years 1940—47 will facilitate appreciation of the figures arrived at in the present study. The population of the district increased during this period from 325 319 to 345 691 and the percentage of the town population from 30.0 to 33.7. The largest town of this district, Borås, a textile center, represented 15 % of the population of the whole district. The birth rate varied between 14.0 % and 18.6 %. The average infant mortality was 2.6 % (2.9 % in the towns and 2.4 % in the country). In 1945 the overwhelming majority (93.7 %) of the births took place in maternity hospitals or the like. Of those infants born during this period 36.4 % belonged to the town population of the district. Of the total number of deliveries registered in the whole district 31.9 % took place at the Maternity Dep't, Borås Hospital, and 43.3 % of the mothers delivered there belonged to the rural population. The admission area of Borås Maternity Dep't, thus covers rather large neighbouring rural districts. There are, however, several rather densely populated industrial communities in these.

### Frequency of Prematurity

During the years 1939—48, 18 099 parturitions took place at the Maternity Dep't of Borås Hospital: 434, or 2.4 %, of these were still-births. Of the live-births 952, or 5.4 %, were prematures. There were 176 premature still-births, representing 15.6 % of

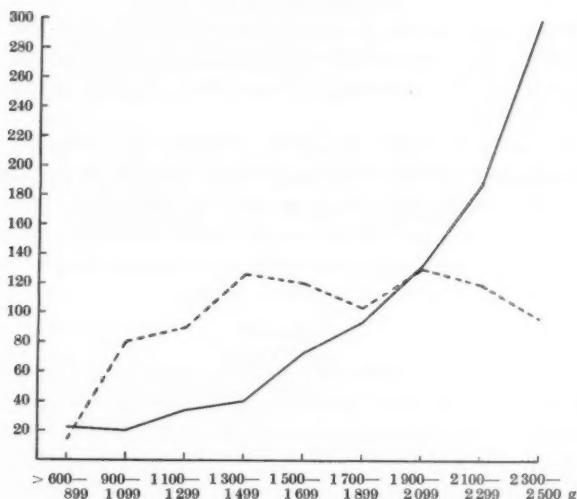


Fig. 1. Frequency of premature infants in the various weight groups.

— live births.  
 - - - still births.

the total number (1 128) of premature deliveries. Of the still-births 40.6 % were prematures. Of the total number of births 6.2 % were thus premature. There was no significant difference in the relative frequency of premature children in different calendar years during this period in spite of a yearly increase in the number of deliveries.

#### Premature Live-Births

The birth-weights of these 952 live-births fell into different groups, as shown in Fig. 1, on which also the curve representing the 176 still-births has been plotted (the group-incidence of these 176 still-births has been multiplied by five to permit the use of a common scale for both curves). Fifty two of the live-births and 5 of the still-births weighed exactly 2 500 g.

In the following table, in which the figures represent percentages, comparisons are made between premature and full-term live-births (17 665).

	Mother				Infant		
	From Country	From Town	Un-married	Married	Twin	Boy	Girl
Premature	44.1 $\pm$ 1.6	55.9 $\pm$ 1.6	17.2 $\pm$ 1.2	82.8 $\pm$ 1.2	20.6 $\pm$ 1.3	47.7 $\pm$ 1.6	52.3 $\pm$ 1.6
Full-Term	43.0 $\pm$ 0.38	57.0 $\pm$ 0.38	8.2 $\pm$ 0.21	91.8 $\pm$ 0.21	1.2 $\pm$ 0.08	51.0 $\pm$ 0.39	49.0 $\pm$ 0.39
Difference	0.8 $\pm$ 1.7		9.0 $\pm$ 1.2		19.4 $\pm$ 1.2		3.3 $\pm$ 1.7

These two groups differ statistically only as regards the incidence of twins and unmarried mothers.

Of the mothers 59.0 % were uniparas, and 55.6 % under 30 years of age.

The calendar years did not differ from one another in the above respects.

### Causes of Prematurity

Only a few obvious conclusions can be drawn from the present series. The higher incidence of twin-births among premature infants has already been pointed out. The relatively high percentage of unmarried mothers might suggest less favourable living conditions as a possible cause, but the social factors were not inquired into. Grave malformations of the infant were found in 35 cases (3.7 %). In 127 cases (13.3 %) the mother was suffering from nephropathy, eclampsism or eclampsia. Premature separation of the placenta occurred in 14 cases and placenta praevia in 18 cases. Finally, other grave diseases of acute or chronic character occurred in the mothers of 31 of the children (3.3 %).

### Mortality Rate

The mortality rate here is to be understood as that percentage of the total number of live-births who died at the Maternity Dep't, or the Pediatric Dep't, before reaching a degree of maturity warranting release. The rate of mortality of the whole material was  $21.6 \pm 1.3$  % (206 infants). The mortality rate in the various weight groups will be apparent from Fig. 2.

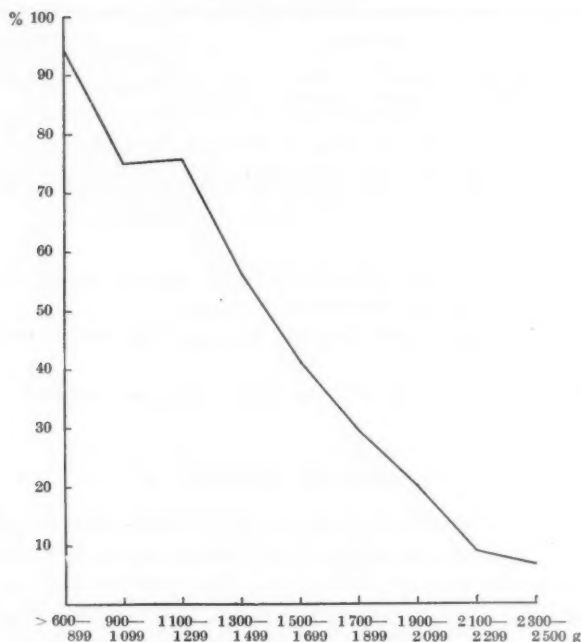


Fig. 2. Mortality in the various weight groups.

Of the infants with a birth weight under 1 500 g,  $72.8 \pm 4.2$  % died, and of those with a birth weight below 1 250 g (immatures, according to YLPPÖ) the death rate was  $84.6 \pm 4.5$  %. The mortality rate of those 52 children that weighed exactly 2 500 g at birth was 3.8 % (2 deaths). One might have expected the mortality rate to decrease with time and increasing experience, new and better therapeutics etc. but no significant differences could be found in this series. If, however, the mortality of children with a birth weight under 1 500 g during the years 1939—43 ( $85.7 \pm 5.4$  %) is compared with that of the years 1944—48 ( $65.3 \pm 5.6$  %) a difference of  $20.4 \pm 7.8$  will be apparent, so that there are signs of an improvement in the mortality rate of these most premature births.

The rate of mortality according to time of survival was:

First hour	2 %
» day	12.3 »
» week	17.9 »
» two weeks	18.6 »
» month	20.4 »
» two months	21.0 »

These death rates did not differ significantly from one calendar year to another.

The mortality as from the fourth day until the second month, inclusively, which may be regarded as an index of the *risk of infection at the hospital*, was 4.7 % (45 deaths).

There was no significant difference in the mortality rate of (a) infants of mothers living in the country and infants of mothers living in towns, (b) infants of uniparas and those of multiparas, (c) illegitimate and legitimate infants, and (d) infants of mothers over 30 years of age and those of mothers under 30 years of age. The mortality in twin births did not differ from that in single births. Of the boys  $26.4 \pm 2.1$  % died, the death rate of the girls being  $17.3 \pm 1.7$  %. The difference was  $9.1 \pm 2.7$  %; thus there was significant preponderance of boys.

#### Causes of Death

Postmortem examination was not made of all of the 206 infants that died, nor was the autopsy made as a rule by a trained pathologist. Nevertheless, it should be mentioned that in 25 cases (12.1 %) there were grave malformations. Infections were responsible in at least 20 cases (9.7 %). Intracranial hemorrhage was considered the cause of death of 18 infants (8.7 %). In 139 cases (67.5 %) the only cause of death noted in the records was "debilitas vitae congenita".

Obstetric intervention was necessary in the 114 deliveries (20 low-forceps, 8 high-forceps, 40 Caesarian section, 20 version + extraction, and 26 rupture of membranes, sometimes with me-treuryis). A higher mortality rate might have been expected

in these cases, but it did not differ from that of the rest of the series. This may possibly be explained by the fact that these operatively delivered infants belonged to the higher weight groups, so that their chance of survival was presumably more favourable from the outset. The 115 breech presentations showed a mortality of  $27.8 \pm 4.2$ , which thus differed from that of the whole material by  $6.2 \pm 4.4$  %.

#### **Nephropathia Gravidarum**

The mothers of 127 children had nephropathy, eclampsism or eclampsia. The mortality of these children was  $13.4 \pm 3.0$  %, differing from that of the entire series by  $8.2 \pm 3.3$  %. In an effort to find an explanation for this ostensibly lower mortality the degree of prematurity was calculated in those 104 nephropathic cases in which information was available, on the basis of the reported day of the last menstruation and a normal length of gestation of 270 days. One hundred and four premature infants born at the Maternity Dep't, immediately after those with nephropathic mothers were selected as a comparative series. Of the mothers with nephropathy, 16 were suffering from eclampsism and 10 from eclampsia at the time of delivery. The mortality of the infants born of nephropathic mothers was  $12.5 \pm 3.2$  % as compared with  $25.0 \pm 4.2$  % of the controls, the difference thus being  $12.5 \pm 5.3$  %. The weight of the infants of these nephropathic mothers was on an average 2 057 g and that of the controls 2 153 g, with an average prematurity of 20 days and 32 days, respectively. Owing to the great standard deviation in this series no significant difference could be demonstrated, but it is conceivable that the apparently lower mortality in infants of nephropathic mothers is ascribable to the more advanced age of the infants at the time of birth. Undernourishment during intrauterine life results in a lower birth weight, but any risks to be expected on account of prematurity and the mother's disease are probably compensated or outweighed by the higher degree of development of the infant at the time of birth. In the interest of the infant, then, premature interruption of the pregnancy of a gravely nephropathic mother for the purpose of delivering what may be termed an ordinary



premature infant instead of the generally thin, dehydrated, "nephropathic" infant is contraindicated. On the other hand, nephropathia gravidarum is one of the commonest causes of premature still-birth (see below), so that it is hard to decide whether or not premature interruption of pregnancy is in the interest of the infant.

### Premature Still-Births

It will be apparent from Fig. 1, in which the incidence of the infants in the various age groups is graphically depicted, that there was a preponderance of premature births in the low age groups. Among the still-births only  $64.8 \pm 3.6$  % weighed more than 1500 g, as compared with  $88.0 \pm 1.0$  % of the live-births.

The following table shows a comparison between live-births and premature still-births (figures represent percentages).

	Mother				Infant	
	Unipara	Un-married	Town Resident	< 30 Yrs. Old	Twin	Girl
Live-Births (952)	$59.0 \pm 1.6$	$17.2 \pm 1.2$	$55.9 \pm 1.6$	$55.6 \pm 1.6$	$20.6 \pm 1.3$	$52.3 \pm 1.6$
Still-Births (176)	$51.1 \pm 3.8$	$10.2 \pm 2.3$	$49.4 \pm 3.8$	$38.1 \pm 3.7$	$9.1 \pm 2.2$	$49.4 \pm 3.7$
Difference	$7.1 \pm 4.1$	$7.0 \pm 2.6$	$6.5 \pm 4.1$	$17.5 \pm 4.0$	$11.5 \pm 2.5$	$2.9 \pm 4.0$

The percentage of twins in the still-birth group is thus smaller and the percentage of mothers over 30 years of age greater. Furthermore, the percentage of illegitimate still-births seems to be smaller.

Certain conclusions may be drawn concerning the *cause of still-birth*. Of the infants 135 (76.7 %) are registered as prepartal deaths, whilst the remaining 23.7 % died in the act of delivery. In 25 cases (14.2 %) the infant was malformed to such a degree that it could not be expected to survive. In 5 cases the mother had diabetes but in only 1 case syphilis. Placentae abruptio occurred in 30 cases (17.2 %) and hydramnion in 10 cases. In no fewer than 40 cases (22 %) *the mother suffered from nephropathy*, eclampsism or eclampsia. Intervention was necessary in 14 cases only.

The percentage of twins among premature still-births was also greater than among the full-term infants. It should also be observed that 10 (16.1 %) of the 62 infants with a birth weight under 1 500 g were illegitimate, whereas only 8 (7.0 %) of the 114 infants with a higher birth weight were children of unmarried mothers. If this difference of 9.1 % is true, attempted abortion may be suspected as a possible cause of premature still-birth.

#### Comparison with Statistics of Other Series etc.

In order to investigate whether the mortality rate at the Maternity Dep't, Borås Hospital, was higher than rates recorded elsewhere, a few figures from some other recent statistical compilations were studied.

During the years 1944—46, ALM found a premature live-birth frequency of 5.63 % (508 infants) and a mortality of 13.6 % for the first day, 20.3 % for the first month, and 22.0 % for the first year at the Allmänna B.B. in Stockholm. The total mortality of three maternity institutions in the district of Stockholm was 3.35 % (131 infants) for the first day, 12.2 % for the first month, and 13.1 % for the first year. HOLMDAHL reported that 76 (26.9 %) of the 283 premature live-births in Gothenburg in 1946 died and that the corresponding figures for 1948 were 47 out of 288 (16.3 %). PARVIAINEN reported a hospital mortality of 33.4 % among 1 622 prematures born in Helsinki between 1928—35 and weighing 600—2 500 g at birth. BOESEN reported a mortality of 26.3 % among 796 prematures born at four Danish hospitals and weighing 1 000—2 499 g, while that of the 234 prematures at most 2 days old admitted to the pediatric department of Copenhagen Hospital the same year was 46.5 %.

Even this brief review shows that the figures vary considerably from one place or country to another. As pointed out in the introduction, it is of importance for investigation of the prognosis of prematurity that nomenclature and registration principles be standardized as soon as possible. The difference between different series from various parts of the world, some of which are at present unnaturally great, cannot be properly judged, nor is

it possible to estimate the part various therapeutic measures play in the decreased mortality of prematures. In accordance with YLPPÖ's proposal the author recommends the following definition: a premature is characterized by a birth weight of 2 500 g or less, and an abortion by a birth weight not exceeding 600 g.

### Summary

The author analyses and discusses a 10 year series of 952 premature live-births from a Swedish district hospital where the percentage of prematures was 5.4 %. The author shows that multiple births are partly responsible for prematurity and that the mothers of prematures are more frequently unmarried. The total mortality at the hospital was 21.6 %, the death rate being 12.3 % for the first day and 17.9 % for the first week. The death rate of boy infants was significantly higher than that of girls. Obstetric intervention did not increase mortality, probably because in intervention cases the infants' birth weights were higher. The mortality rate of the infants of mothers with nephropathia gravidarum seemed lower, presumably because of longer intra-uterine life.

The author also reports 176 premature still-births from the same period, but with a weight distribution different from that of the live-births and a lower percentage of multiple births. The mothers of still-births were relatively older and more frequently married. Nephropathia gravidarum was present in the mothers of 22.7 % of the still-births.

Finally, the results are compared with the figures of earlier authors. The author recommends standardization of relevant definitions and registration methods so that the true prognosis of the premature may be established and the efficacy of modern therapeutic measures judged. YLPPÖ's nomenclature is recommended.

### Résumé

L'auteur analyse et discute une série de dix ans comprenant 952 cas de naissance avant-terme d'enfants vivants dans un hôpital de district suédois où le pourcentage des accouchements

avant-terme était de 5,4. L'auteur démontre que les naissances multiples sont en partie la cause d'accouchements prématurés et que les mères d'enfants nés avant-terme le plus souvent ne sont pas mariées. La mortalité totale à l'hôpital était de 21,5 %, le pourcentage étant de 12,3 % pour le premier jour et de 17,9 % pour la première semaine. Le pourcentage de décès des enfants mâles était sensiblement plus élevé que celui des filles. Les interventions obstétricales n'ont pas augmenté la mortalité, probablement parce que dans les cas d'intervention le poids des enfants à la naissance était plus élevé. Le pourcentage de mortalité chez les enfants de mères atteintes de néphropathia gravidarum semblait plus bas, probablement à cause de la période plus longue de vie intrautérine.

L'auteur rapporte aussi 176 cas de naissance avant-terme d'enfants mort-nés pendant la même période, mais présentant une répartition de poids différente de celle des naissances d'enfants vivants et un pourcentage plus bas de naissances multiples. Les mères d'enfants mort-nés étaient relativement plus âgées et plus fréquemment mariées. On a constaté de la néphropathia gravidarum chez les mères de 22,7 % des enfants mort-nés.

Finalement on établit une comparaison avec les résultats et les chiffres obtenus par des auteurs antérieurs. L'auteur recommande la standardisation des définitions pertinentes et des méthodes d'enregistrement afin de permettre une prognose juste des cas de naissance avant-terme et de juger de l'efficacité des mesures thérapeutiques modernes. On recommande la nomenclature d'YLPÖ.

#### **Zusammenfassung**

Der Verfasser analysiert und diskutiert eine 10-Jahresreihe von 952 lebenden Frühgeburten von einem schwedischen Distriktkrankenhaus, in dem der Prozentsatz Frühgeburten 5,4 betrug. Der Verfasser weist nach, dass Vielgeburten teilweise die Ursache von Frühgeburten sind und dass die Mütter bei Frühgeburten häufiger unverheiratet sind. Die Gesamtsterblichkeit betrug im Krankenhaus 21,6 %, wobei die Sterblichkeit 12,3 % für den ersten Tag und 17,9 % für die erste Woche betrug. Die Sterblich-

keit war bei Knaben auffallend höher als bei Mädchen. Obstetrischer Eingriff erhöhte nicht die Sterblichkeit, vermutlich da in Eingriffsfällen das Geburtsgewicht des Kindes höher war. Die Sterblichkeit schien für Kinder von Müttern mit *nephropathia gravidarum* geringer zu sein, anscheinend auf Grund längeren intrauterinen Lebens.

Der Verfasser berichtet auch über 176 Früh-Tod-Geburten aus der gleichen Periode, jedoch mit einer Gewichtsverteilung, die sich von der bei den Lebendgeburten unterscheidet und mit einem geringeren Prozentsatz Vielgeburten. Die Mütter waren bei Todgeburten verhältnismässig älter und häufiger verheiratet. *Nephropathia gravidarum* war bei den Müttern von 22,7 % der Todgeburten festgestellt.

Schliesslich werden die Resultate mit den Zahlen früherer Verfasser verglichen. Der Verfasser empfiehlt Normung von bedeutungsvollen Definitionen und Registrierungsmethoden, so dass die richtige Prognose der Frühgeburt gestellt und die Wirksamkeit moderner therapeutischer Massnahmen beurteilt werden kann. Die Nomenklatur des YLPPÖ wird empfohlen.

### Resumen

El autor analiza y discute un período de diez años comprendiendo 952 casos de niños nacidos antes de término en un hospital de distrito sueco, donde el porcentaje de partos prematuros alcanzaba el 5,4 %. El autor demuestra que los nacimientos múltiples son en parte la causa de partos prematuros y que las madres de los niños nacidos antes de término corrientemente no están casadas. La mortalidad total en el hospital era del 21,5 %, correspondiendo al primer día el 12,3 %, y el 17.9 % a la primera semana. El porcentaje de fallecimiento de niños varones era sensiblemente más alto que el de niñas. Las intervenciones obstétricas no han aumentado la mortalidad, probablemente porque en los casos de intervención el peso de los niños al nacer era más elevado. El porcentaje de mortalidad en los niños de madres atacadas de *nephropathia gravidarum* parecía más bajo, probablemente a causa del período más largo de vida intrauterina.

El autor reporta también 176 casos de nacimientos antes de

término de niños nacidos muertos durante el mismo período, pero presentando una distribución de peso diferente a la de los nacimientos de niños vivos y un porcentaje más bajo de nacimientos múltiples. Las madres de los niños nacidos muertos eran relativamente de más edad y con más frecuencia casadas. Se ha comprobado la nephropathia gravidarum en las madres del 22,7 % de los niños nacidos muertos.

Finalmente se establece una comparación con los resultados y las cifras obtenidas por autores anteriores. El autor recomienda la generalización de definiciones pertinentes y de los métodos de registro, a fin de permitir un pronóstico justo de los casos de nacimiento prematuro y poder juzgar la eficacia de las medidas terapéuticas modernas. Se recomienda la nomenclatura de YLLPÖ.

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## **Häufigkeit der akuten schweren Tuberkulose bei Kindern mit und ohne BCG-Schutzimpfung**

Von

**K. FRANK**

Die zahlenmässige Auswertung des praktischen Erfolges der BCG-Schutzimpfung ist schwer. Diesbezügliche Untersuchungen können nur dann von absolutem Wert sein, wenn wir die Zahl der Erkrankten unter den Schutzgeimpften mit der Zahl der unter der Kontrollgruppe vergleichen, die unter gleichen Umständen lebte, ohne schutzgeimpft zu sein. Die vergleichenden Untersuchungen von ARONSON (1) bei Indianern, die von FERGUSON (2) in Kanada, von HYGGE (3) an dänischen Studenten und von NORDVALL (4) an schwedischen Pflegerinnen können heute als die exaktesten diesbezüglichen Angaben betrachtet werden.

Zur mutmasslichen Auswertung gilt als beste Methode die Feststellung, in welchem Masse die schutzgeimpfte Kinderbevölkerung von Streuung und besonders von Gehirnhautentzündung befallen wird im Verhältnis zu der nichtgeimpften.

Nach J. HOLM (5) kam in Dänemark seit dem Jahre 1938 bei Schutzgeimpften unter dem zweiten Lebensjahr kein einziger Fall von tuberkulöser Gehirnhautentzündung vor.

Bevor wir auf die Einzelheiten unserer eigenen Beobachtungen eingehen, müssen wir von der Schutzimpfung im Allgemeinen bemerken, dass diese nicht immer eine absolute Immunität zur Folge hat. Es soll nur in 95 % der Fälle eine Allergie angetroffen werden (ANDERSON (6)). An unserem Material sind die nachträglichen Tuberkulinproben zur Feststellung der Allergie noch nicht vorgenommen worden.

Im Zusammenhang mit den Schutzimpfungen, welche im Frühjahr 1948 in Südungarn vollzogen wurden, haben wir in der

Perspektive des verflossenen Jahres unser klinisches Material in Hinsicht auf die Wirksamkeit der Impfung geprüft.

Wir haben Folgendes in Betracht gezogen:

1) Wie gross der Prozentsatz der Fälle mit Bazillartuberkulose seit 1948 bei den schutzgeimpften Kranken auf unserer Kinderklinik in Pécs ist, denjenigen gegenüber, die keine Schutzimpfung erhielten.

2) Ebenso verglichen wir jene Fälle, die mit akuter pulmonaler Streuung auf unsere Klinik aufgenommen wurden.

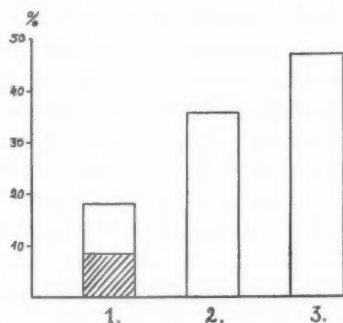
### **1) Verhältnis der Bazillartuberkulosefälle bei Schutzgeimpften und Ungeimpften seit der Impfung von 1948**

Das Gros der Schutzimpfungen lief im Monat April des Jahres 1948 ab. Vorangehend beobachteten wir 6 Fälle, demnach können von den im Jahre 1948 behandelten 33, an tuberkulöser Hirnhautentzündung leidenden Kranken 27 als solche betrachtet werden, die nach der Impfungsperiode erkrankten; in den ersten fünf Monaten von 1949 waren deren 18, zusammen werden also 45 Fälle den Gegenstand unserer Prüfungen bilden. Weiterhin werden wir also unsere Folgerungen in Bezug auf diese Fälle ziehen.

Von den 45 an Mening. tbc. Leidenden erhielten vorher nur 8 eine BCG-Impfung, was 17,7 % ausmacht. Anlässlich der obligaten Prüfung auf Tbc. wurden 16 (35,6 %) tuberkulös positiv befunden, die übrigen 21 (46,7 %) sind der behördlichen Kontroll- und Schutzimpfungstätigkeit entgangen. Diese Verhältnisse werden in folgender Figur veranschaulicht.

In Anbetracht dessen, dass in Sündungarn die erwachsene Bevölkerung inbegriffen, ca. 95 % der Gesamtbevölkerung auf Tbc. geprüft werden konnte und die Mehrzahl der Kinder (54 %) auch geimpft worden ist, können wir uns leicht vorstellen, dass die Zahl derjenigen, die den Tuberkulinproben und der Schutzimpfung entgangen waren, nur eine geringe sein kann. Dass aber diese Wenigen trotzdem den Prozentsatz von 46,7 der Meningitiden bilden, gegenüber den Geimpften, deren Prozentsatz sich auf 17,7 beläuft, daraus kann nur jene Folgerung gezogen werden, dass das Kleinkindalter für Mening. tbc. ohne Schutzimpfung viel-





Verhältnis der Meningitis Fälle mit und ohne Schutzimpfung.

Die Höhe der ersten Säule zeigt den Prozentsatz der schutzgeimpften, jene der zweiten den Prozentsatz der bei der Tuberkulinkontrolle bereits positiv gefundenen, jene der dritten Säule den der nicht tuberkulinierten bzw. nicht geimpften Fälle.

Der schraffierte Teil der 1. Säule zeigt die Zahl derjenigen, die nach der Schutzimpfung dauernd in einer Umgebung von offener Tbc., ständiger Infektion ausgesetzt, lebten.

fach empfänglicher ist. — Betrachten wir aber die Angaben von HOLM (5), dann finden wir, dass in Staaten, wo die hygienischen Verhältnisse in Bezug auf tuberkulöse Erkrankungen günstiger sind, bei schutzgeimpften Kindern Bazillartuberkulose überhaupt nicht mehr vorkommt. Im Vergleich zu dieser Tatsache wäre unser Prozentsatz von 17,7 schlimm genug.

Nach den Grund dieser noch immer ungünstigen Proportionalität forschend, führten wir bei schutzgeimpften Kranken Umgebungsuntersuchungen durch. Sowohl aus diesen, wie auch aus den nachträglich eingelaufenen Meldungen der behandelnden Provinzärzte, konnten wir feststellen, dass von den 8 schutzgeimpften Kindern 4 ständig in solchen Familien lebten, wo offene Tbc vorhanden war. Gegen solche massive Infektionen kann die BCG-Impfung im Kleinkindalter keinen absoluten Schutz bieten. Nur 8,8 % der geimpften Fälle erlag daher einer Infektion von unbekannter Herkunft und Intensität. Von den übrigen Fällen sind auch 2 solche, bei denen wir in der unmittelbaren Familie von einer an offener Tuberkulose gestorbenen Person wissen, fernerhin einer, der 4 Wochen nach der Impfung an Masern erkrankte, wonach die Streuung festgestellt werden konnte. Bei

diesen Fällen können wir voraussetzen, dass die Technik der Tbc-Filtration vielleicht nicht einwandfrei gewesen war. Demzufolge bleibt eigentlich nur ein einziges geimpftes Kind, dessen Infizierung auch weiterhin als offene Frage besteht.

Dessenungeachtet ist aus den vorhergegangenen Angaben die schlagende Tatsache festzustellen, dass 5/6 der Meningitis-Fälle an solchen Kindern auftrat, die keine BCG-Schutzimpfung erhielten, und nur 1/6 kann den Geimpften zugeschrieben werden.

## **2) Verhältnis der akuten schweren pulmonalen Fällen bei Schutzgeimpften und Ungeimpften**

Es ist notwendig, dass wir die akuten schweren Fälle von pulmonaler Streuung ebenfalls einer genauen Prüfung unterziehen. Um etwaige Subjektivität zu vermeiden, besprechen wir nur solche Kranke die laut Verordnung des Volkswohlfahrtsministeriums mit Streptomycin behandelt werden sollten und konnten. Es handelt sich um 27 Fälle, bzw: 1 Fall von miliarer Tuberkulose, 18 mit bronchogener Dissemination, 5 Schwerkranke mit frischer einseitiger Infiltration, 1 ebenfalls schwerer Fall mit einer ulcerierten Drüse tuberkulösen Charakters, 1 Fall von Kehlkopftuberkulose und ein an tuberkulöser Peritonitis leidender unter zwei Jahren.

Von den an schwerer Tuberkulose leidenden erhielten 4 die BCG-Impfung (14,8 %). Bei den Filtrierungen waren davon 12 (44,4 %) Pirquet positiv und 11 sind der behördlichen Tuberkuloseprüfung entgangen.

Unter Bezugnahme auf die oben erörterten Beweisgründe, kann festgestellt werden, dass von der grossen Zahl der Geimpften nur 14,8 %, von der geringen Zahl der Nichtgeimpften aber 40,8 % von schwerer akuter Lungentuberkulose befallen wurden; der grosse Unterschied des Prozentsatzes beweist demnach ausdrücklich die Schutzkraft der BCG-Impfung.

Die Forschungen betreffs der unmittelbaren Umgebung der mit BCG geimpften ergibt ähnliche Verhältnisse, wie bei der Meningitis besprochen: Ein zweijähriges Kind lebte wochenlang mit seinem Grossvater, der an offener Tuberkulose mit tödlichem

Ausgange litt; ein anderer Säugling von neun Monaten wurde erst geimpft, als seine Mutter schon einen Monat lang mit Pneumothorax behandelt wurde, der Vater des Kindes litt auch an Tbc, so traf den Säugling die Impfung unbedingt in der Inkubation der Infektion. Ein Kind vom Asyl bekam kurz nach der BCG-Impfung Keuchhusten, bald darauf wurde eine tuberkulöse Fistel wahrgenommen, also erfolgte die Infizierung gleichfalls in einer anergischen Phase. Auch hier ist also die Entstehung der Streuung durchaus verständlich.

Unsere Angaben widerlegen die auf nicht objektiven Wahrnehmungen beruhenden Beschuldigungen, die den BCG-Impfungen eine Meningitis hervorrufende und aktivierende Wirkung zuschreiben. Selbstverständlich kommen Streuungen bei Geimpften vor, aber deren Prozentsatz ist verschwindend klein im Verhältnis zu den Nichtgeimpften. Kommt es bei den Geimpften zur Streuung, so kann auch fast immer ein massiver, ständiger, intrafamiliärer Krankheitsherd nachgewiesen werden. Von der Impfung können wir keinen vollkommenen Schutz erwarten (WALLGREN (7)). Ein solcher Grad der Immunität ist aber gewiss erreichbar, wie bei Personen mit positiver Reaktion, die eine wirkliche Infektion optimal durchgemacht haben (HEIMBECK (8)). Impfungen in grosser Zahl haben qualitative Änderungen zur Folge (HAVAS (9)). Die BCG-Impfungen schützen das Kleinkind vor täglich vorkommenden oberflächlichen Infekten aber eine massive Infektion wird auch weiterhin naturgemäss Erkrankungs Vorgänge hervorrufen.

### **Zusammenfassung**

Die von uns beobachteten Fälle von Bazillartuberkulose kamen nur in einem Prozentsatz von 17,7 bei den mit BCG geimpften vor. Die Hälfte letzterer lebte nach der Impfung längere Zeit in einer familiären Umgebung mit offener Tuberkulose. Obwohl 95 % der Bevölkerung auf Tuberkulose geprüft wurden und der grösste Teil der negativ reagierenden auch der Schutzimpfung teilhaft war, stammen trotzdem die 46,7 % der Gehirnhautentzündungen von jenem verschwindend kleinen Teil der Kinderbevölke-

rung her, welcher sich der behördlich vorgeschriebenem Tuberkuloseprüfung und Impfung entzog.

2) Unter den mit Streptomycin behandelten schweren akuten Fällen von Lungentuberkulose waren auch nur 14,8 % mit BCG geimpfte Fälle.

3) Beim grössten Teil der geimpften, aber trotzdem an Meningitis oder akuter Streuung erkrankten Kindern ist es nachgewiesen worden, dass diese nach der Impfung einer massiven intrafamiliären Infektion ausgesetzt waren.

### Summary

1) The cases of basal tuberculosis which we observed occurred in only 17.7 % of the BCG-inoculated. Following inoculation half of the latter lived for a relatively long period with people who had open tuberculosis. Although 95 % of the population was tuberculin-tested and the majority of those with negative reactions were inoculated, nevertheless 46.7 % of the meningitis cases occurred among the infinitesimal number of children who eluded the tuberculin tests and inoculation prescribed by the authorities.

2) Among the severe acute cases of pulmonary tuberculosis treated with streptomycin, only 14.8 % were BCG-inoculated.

3) It has been shown that the majority of inoculated children who nevertheless contracted meningitis or acute miliary tuberculosis were exposed after the inoculation to massive familial infection.

### Résumé

1) Les cas de tuberculose basilaire observé par nous ne se sont présentés que dans un pourcentage de 17,7 chez les sujets vaccinés au BCG. La moitié de ces derniers ont vécu assez longtemps après la vaccination dans un milieu familial présentant de la tuberculose ouverte. Bien que 95 % de la population ait été soumise à l'examen de la tuberculose et que la majeure partie des sujets réagissant négativement aient été vaccinés préventivement, il n'en reste pas moins que 46,7 % des méningites proviennent de la partie infime de la population enfantine qui s'est soustraite à l'examen et à la vaccination contre la tuberculose prescrits par les autorités.

2) Dans les cas graves de tuberculose pulmonaire aiguë traités à la streptomycine, il y avait seulement un pourcentage de 14,8 de cas vaccinés au BCG.

3) Dans la plupart des cas où des enfants vaccinés ont quand même été atteints de méningite ou de dispersion aiguë, on peut démontrer que ceux-ci après la vaccination ont été exposés à une infection intrafamiliale massive.

### Resumen

1) Los casos de tuberculosis basilar que hemos observado no presentan más que un 17,7 % de sujetos vacunados al BCG. La mitad de estos últimos han vivido un tiempo bastante largo después de la vacunación en un medio familiar que presenta la tuberculosis abierta. A pesar de que el 95 % de la población haya sido sometida al examen de la tuberculosis y que la mayor parte de los individuos resistentes negativamente hayan sido vacunados preventivamente, ello no obstante el 46,7 % de las meningitis provienen de la parte ínfima de la población infantil que se ha sus- traído al examen y a la vacunación contra la tuberculosis prescritos por las autoridades.

2) En los casos graves de tuberculosis pulmonar aguda tratados con la estreptomycinina, ha habido solamente un porcentaje de 14,8 en cuanto a casos vacunados al BCG.

3) En la mayor parte de los casos en que, a pesar de todo, los niños vacunados han sido atacados de meningitis o de dispersión aguda, se puede demostrar que después de la vacunación han estado expuestos a una infección masiva interfamiliar.

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## A Follow-Up Study of 30 Cases of Lues Congenita Praecox From 2 to 19 Years After Treatment With Acetarsol

by

GUNNAR NYHUS

In 1921 and during the following years, the investigations of FORNEAU, LEVADITI, OPPENHEIM, TRÉFOUEL and others showed that acetarsol (spirocid, stovarsol) had quite considerable spirochaetocide properties and was an excellent remedy for syphilis. It was greeted with enthusiasm particularly because it could be given by mouth.

*Dosage.* Perusal at the present time of the bulky literature on the treatment of congenital syphilis with acetarsol impresses the reader with the great differences of opinion over dosage, both with regard to the size of the daily dose, the duration of a course of treatment and the total dose of one course. On the whole, dosage in the U. S. A. has been very cautious. According to the BRATUSCH-MARRAIN method one gives 1 g per kg body weight in the course of 63 days, repeated twice or oftener, and according to the MAXWELL & GLASER method 14 g in the course of 49 days, repeated thrice. On the other hand, bigger doses based largely on the ERIC MÜLLER method (see Table I) have been given in Central Europe and Scandinavia.

Table I

$\frac{1}{2}$ tablet daily for 10 days	4 days' pause	1 tablet daily for 10 days	4 days' pause	1 $\frac{1}{2}$ tablets daily for 10 days	4 days' pause	2 tablets daily for 10 days
	4 days' pause	3 tablets daily for 10 days	4 days' pause	4 tablets daily for 10 days	4 days' pause	4 tablets daily for 10 days

In the course of 94 days 40 g acetarsol are given.

It may be assumed that this difference in dosage is the main reason why acetarsol has come to be regarded in Europe as an excellent and very suitable anti-syphilitic drug, whereas in the U. S. A. in particular well known syphilis specialists maintained up to only a few years ago that it does not deserve to rank among the adequate anti-syphilitic drugs. Another important reason for this opinion seems to be that the Americans give the drug to older children also, although it was established early that acetarsol is best *suited to infancy, particularly earliest infancy*.

Several follow-up investigations of acetarsol-treated patients have been carried out from time to time, but none of them has concerned patients with an interval of many years between treatment and re-examination.

Acetarsol was given for the first time at the Children's Department of the Rikshospital in Oslo in 1929, the German »Bayer» preparation spirocid being given in most cases. During the first couple of years this treatment was extended tentatively to older children, but it was found that here, as at other hospitals, the effect became more uncertain at the more advanced ages. The drug was therefore soon restricted to infancy. During the first one and one half years the drug was given in intermittent weekly courses, with an interval of a week between the series. The daily dose of  $\frac{1}{2}$  a 0.25 g tablet was given during the first two—three series, after which 1 tablet was given daily, the course lasting from 9 to 15 weeks including the weekly intervals. Thus the total dosage per course came to vary between 6—12 g. The patient was given two or more such courses over a period of one—two years.

Since the middle of 1931 spirocid has been given according to MÜLLER's method of dosage. But attention has always been paid to the patient's general condition, debilitated children being given a more cautious initial dosage. The total dose of spirocid was between 40 and 48.75 g.

During the period September 1929—September 1945, spirocid was given to 52 children who suffered from congenital syphilis and who were under the age of 1 year. Their ages in weeks at the beginning of treatment were as follows:

Table II

Weeks: 1-3-4-6-7-8-9-10-11-12-13-14-15-16-17-19-20-22-23-24-34-35-39

Number: 2-3-3-3-2-2-2-2-4-8-4-1-3-4-1-1-1-1-1-1-1-1-1  
= 52

The following are the most important manifestations of syphilis observed alone or in conjunction with other such manifestations on admission to hospital:

Table III

Coryza.....	41	cases with	14	deaths
Exanthems.....	32	" "	8	"
Pemphigus syphiliticus.....	2	" "	1	"
Swelling of the lymphatic glands.....	15	" "	6	"
Enlargement of the abdomen.....	16	" "	9	"
Enlargement of the liver.....	44	" "	15	"
Enlargement of the spleen.....	42	" "	14	"
Radiologically demonstrated congenital syphilitic changes in the bones (of 44 examined)	42	" "	9	"
Parrot's osteochondritis.....	11	" "	2	"
General oedema.....	3	" "	3	"
Syphilitic eye ground changes (of 38 examined)	15	" "	1	"
Syphilitic nephritis.....	15	" "	6	"

*The cerebrospinal fluid* was examined in 16 cases. It is remarkable, to judge by the literature on the subject, that in the present material the cerebrospinal fluid was normal with regard to cells, protein and the Wassermann reaction with only one exception.

Six of the 11 *premature* children admitted to hospital died, and of the 37 whose general condition was bad on admission to hospital, 13 died.

*Blood Examinations.* Anaemia (haemoglobin under 70 %) was found in 30 out of 44 patients, 8 of whom died. The index was hyperchrome in 4, isochrome in 4, and hypochrome in 22 cases. The percentage of haemoglobin was often very low, right down to 21 %, and in these cases the clinical picture was often that of severe syphilis. The leucocytes were examined in 43 cases, and leucocytosis (over 14,000 per mm<sup>3</sup>) was found in 24 cases, with figures up to 38,400 per mm<sup>3</sup>. A definitely *infectious* blood picture was seen in only 17 of these 43 cases. It is generally assumed that a leucocytosis with shift to the left will always be found in congenital syphilis, at any rate when the syphilitic manifestations are quite plain. But this teaching is not supported



by the present investigation, although the same patient was often examined several times. Leucopenia was found in 3 cases, in one case right down to 2,300 leucocytes.

The sedimentation rate of the erythrocytes was examined in 48 cases and found with only two exceptions to be raised. In 15 cases it was more than 100 mm per hour (Westergren). There was no demonstrable connection between the degree of this rate on the one hand and the leucocytosis and shift to the left on the other.

Reviewing the above-mentioned findings, it may be noted that in the present study also the radiologically demonstrable changes in the bones were found to be the most common and reliable manifestation of congenital syphilis in infancy. Such radiological findings were recorded in all but 2 of the 44 cases radiologically examined.

*Treatment.* This was started at once when the patients presented definite signs of congenital syphilis on admission to hospital, neither proteinuria nor haematuria being regarded as contra-indications. In the absence of definite manifestations of syphilis, the findings of serological tests (Wassermann, Wadsworth-Brown) were awaited first. The serological tests were negative in a 7 day old infant with syphilitic osteochondritis. Finding no reason for inaction on this evidence, we gave the ordinary course of spirocid treatment. After a few days of it, a typically syphilitic rash appeared on the palms of the hands and soles of the feet.

Fifteen of the 52 children died under this treatment, the deaths in 7 of these cases being traceable to malignant visceral syphilis. The other 8 deaths were due to acute, non-specific complications.

In 3 cases the treatment was not completed, and in the remaining 34 cases the treatment given was adequate.

*Complications.* To judge by the literature, the frequency of complications due to the drug ranges from 0 to 8—10 %. In most cases they pass off rapidly after the drug is withheld. At the very beginning of a course of acetarsol, usually after the first dose, it is not rare to find the temperature rising, often vomiting,

diarrhoea and a transient rash. These manifestations pass off quickly, even when the drug continues to be given, and as they are harmless they must not be allowed to discredit this drug. Severe complications and even several deaths have, however, also been recorded. On the whole, it would seem that emphasis on the toxicity of acetarsol is most noticeable in American quarters, in which this drug is regarded as very nephrotoxic.

What is striking in our material is freedom from complications. No patient showed signs of injury to the kidneys during this treatment. The only complications observed, and they always appeared after the first or the two or three first doses, were a rise in temperature in 17 cases, vomiting in 14, and diarrhoea in 10. Two or all three of these phenomena usually affected the same patient, and they were observed in altogether 23 different patients. The rise in temperature was always moderate and lasted a day or two. In a couple of cases it recurred during a second course of treatment and lasted two or three days. The vomiting was slight, seldom occurring more than once a day and lasting only a few days. The diarrhoea was no worse than that the stools were somewhat more frequent and loose for some days than they had been before the treatment was started.

One of the children receiving inadequate treatment developed a flaccid quadriplegia with loss of reflexes after 18.75 g of spirocid had been given. The drug was withheld and the paresis passed off slowly. It cannot be said with certainty whether the paresis was due to the drug or to the syphilis itself. On examination five years later, the patient presented considerable psychic debility with severe spastic paresis of the lower limbs.

In nearly every case the tonic effect of the spirocid was very noticeable.

The sedimentation rate fell rapidly in most cases, but occasionally there was at first a short rise. This rate ran parallel with the serological reactions, and when they were negative on completion of treatment, the sedimentation rate had also, as a rule, fallen to normal or was only slightly raised. But when one or other of the serological reactions was still positive, the sedimentation rate was also raised.

The influence exerted by the treatment on the *congenital syphilitic changes in the bones* was most interesting. When these changes in the bones had given rise to clinical manifestations in the form of pseudopareses, these disappeared in a few days. The radiologically demonstrable changes often became much more noticeable during the first two or three weeks of the treatment, and this was always the case when the changes in the bones were particularly well marked. In skiagrams taken some years ago this finding used to be interpreted as indicating aggravation of the congenital syphilitic inflammation. What they actually did portray was improvement due to the incipient reabsorption of the inflamed tissues with increased calcification. At the completion of the courses of treatment in our material, the bony changes due to congenital syphilis showed healing in every case in which they had not at the outset been very marked. After another month or two, there were no demonstrable radiological changes in any of our cases.

*Serological Reactions.* Among the 30 patients given treatment according to Müller's method there were 19 who were seronegative during or just after a course of treatment, whereas 11 showed a faintly positive Wassermann and/or M. K. R. II in the blood. Three of these 11 were given a second course of Müller's method, after which they were all seronegative. A fourth patient, who was Wassermann-positive at the end of a course and three to four months later, became negative after neobismuth treatment. Among the remaining 7 patients 5 were found to be seronegative at the next examination from one to eight months after completion of the treatment. It would therefore seem that we are justified in counting on seroreactions' often not becoming negative till a few months after completion of treatment. As for the 2 last who were faintly Wassermann-positive at the end of the treatment, one of them never returned for re-examination, while the other did not return till three years later when the Wassermann reaction was still faintly positive. It was not till 16 years later that a new examination was made, and the patient was then seronegative. Of the 4 patients receiving intermittent weekly

courses of treatment, 3 were already seronegative after an eight-weeks' course, and the fourth after two courses.

The greatest quantity of spirocid given in any case was 80 g divided between two courses according to Müller's method. The smallest quantity was 18.5 g divided between two intermittent weekly courses. As serological tests were not carried out systematically during the treatment, we cannot say exactly how much spirocid was needed to render the serological tests negative. The results of the few serological tests carried out during treatment indicate that the serological reactions often became negative before treatment was ended. The smallest quantity of spirocid rendering these tests negative was 5 g, and they often became negative after 15, 20, or 25 g.

*The Follow-Up Examinations.* Among the 34 patients receiving adequate sporocid treatment, 1 was excluded because he subsequently received another form of treatment. The remaining 33 patients, who received only spirocid treatment, were summoned for re-examination 2—18 years after the completion of this treatment. Thirty of them presented themselves for re-examination.

The following data concern the 3 patients not presenting themselves for re-examination. One of them was admitted to the Department 27 days old, with cutaneous and visceral syphilis and in a poor general condition. He was quite fit after the completion of a course of 40 g of spirocid. The liver and spleen were still enlarged, but the serological tests were negative, and they were found to be so still one and one half and three and one half months later. Five months after the completion of treatment, he died in hospital of pneumonia. The post-mortem examination showed no sign of the syphilis from which he had suffered apart from histological changes indicative of an old infection in the liver and spleen.

The second patient receiving adequate treatment was admitted to hospital 3 months old suffering from syphilis of the cutaneous, visceral and bony systems. After a modified course of Müller's method with only 26.25 g of spirocid, the patient became symptom-free and Wassermann-negative. The local doctor reported that the child always enjoyed good health and developed normally. The serological tests, repeated for several years, were always negative. This year the patient passed a higher school examination (realskoleeksamen).

The third patient receiving adequate treatment developed syphilitic pemphigus when 8 days old and was admitted to hospital 26 days old.

This was a case of third generation syphilis, the mother having been treated for parenchymatous keratitis when 8 years old. The patient received 41.25 g of spirocid in one course. The serological tests became negative after only 11.75 g of spirocid and were negative at two subsequent examinations, the last being made four and one half months after the completion of the course. The child is now 11 years old and perfectly fit. The mother was therefore of the opinion that a re-examination was superfluous.

Thus we have grounds for concluding that the disease was cured in these 3 cases.

Table IV gives the number of years between treatment and follow-up examination.

*Table IV*

Re-examination after:	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	years.
Number of patients:	3	2	1	1	0	0	1	1	3	2	0	3	2	3	2	3	3	

Care was taken to make this follow-up examination as complete as possible. The patients were admitted to the Children's Department of the Rikshospital or to its Medical Department B. To begin with the patients underwent a general examination including a careful search for syphilitic stigmata. Special examinations were then made at the Eye, Neurological and Ear, Nose and Throat Departments. All four limbs were radiologically examined in their entirety and with lateral exposures of the tibia, as was the cranium, a teleröntgenogram being taken of patients over the age of 12 years. A complete examination of the blood was made with a differential leucocyte count, measurement of the sedimentation rate, and the serological reactions (Wassermann and M. K. R. II.). The cerebrospinal fluid was examined in every case (protein reactions, cell counts and Wassermann). The patient who as an infant had presented a positive Wassermann reaction and a high cell count was also subjected to an encephalographic examination. A thorough examination was made of the urine, and all the patients were finally submitted to intelligence tests — the so-called Oslo tests devised by Dr. Lofthus.

On re-examination, 29 had a record of uninterrupted good health. One expatient had been admitted to a home for mental defectives and had been subject to convulsions with loss of consciousness. The findings of this follow-up examination may be summarized thus.

Table V

Ordinary general examination, neurological examination excepted. Height and weight. Special examination at Eye Department. Special examination at Ear, Nose and Throat Department. Complete blood examination, with sedimentation rate.	Normal findings in every case.
Radiological examinations.	All normal apart from doubtful case of saber shin.
Special examination at Neurological Department.	Normal in 28, spastic paresis in 2 cases.
Examination of urine.	Normal in 29 cases, proteinuria in 1.
Wassermann and M. K. R. II in the blood.	Serologically negative in 29, positive in 1.
Examination of cerebro-spinal fluid.	Normal in 29 cases Wassermann positive, raised cell count and positive protein reactions in 1 case.
Encephalographic examination in 1 case.	Nothing pathological.
Changes in skull.	None.
Stigmata of congenital syphilis.	Hutchinson's teeth: 4 of a possible 23. Saber shin: 1 (?).

None of the patients presented eye ground changes, although there had been 10 cases of chorioretinitic changes in infancy. Parenchymatous keratitis was not found in any case and there was no history of other diseases of the eyes. Among the stigmata of congenital syphilis there were as many as 4 cases of Hutchinson's teeth, and as only 23 of the re-examined patients had their permanent front teeth in the upper jaw, it is surprising that so

many developed Hutchinson's teeth in spite of the serological reactions' being negative. This observation confirms the teaching that infection in early foetal life is of importance to the development of Hutchinson's teeth.

Two patients presented on re-examination a spastic paresis of the lower limbs. Spastic diplegias are no rare manifestation of cerebral disease in congenital syphilis. The anatomical basis for these may already have been established in intrauterine life or in the early post-natal period without having given rise to clinical manifestations at the time. On the other hand, it is also alleged that children with congenital syphilis at birth are more liable to suffer traumatic injuries to the brain during birth than other infants, since pathological-anatomical changes in the blood vessels have rendered them abnormally brittle (C. HOCHSINGER). Proof positive of this teaching has yet to be produced. In our opinion syphilitic hepatitis may predispose to hypoprothrombinaemic haemorrhages. We have been unable to find any record of prothrombin investigations of newborn infants suffering from congenital syphilis.

One of the patients with spastic paresis, a twin, was a case of premature birth with a breech presentation. Labour was precipitate when the other patient with spastic paresis was born. It is therefore conceivable that in both these cases the spastic diplegia may have resulted from injury to the brain during birth and had nothing to do with syphilis.

Proteinuria was found on re-examination of an 18 year old lad who had also suffered from proteinuria and haematuria in infancy. But his urine had been normal on his discharge from hospital and on subsequent occasions. He had, however, suffered from acute nephritis after an angina faucium seven years before the follow-up examination.

The radiological examination of the limbs showed normal conditions in every case apart from a somewhat doubtful case of saber shin. Even the most pronounced bony changes due to congenital syphilis had disappeared completely.

The serological reactions were positive in only one case, in which they were so in both blood and cerebrospinal fluid. This

patient had been admitted to hospital when 5 months old for congenital syphilis of medium severity. He tolerated the 48.75 g of spirocid given in one course quite well, after which the Wassermann reaction was still faintly positive. At the follow-up examination when he was 12 years old, no outstanding clinical or radiological evidence of syphilis could be found and the blood picture was normal. His intelligence quotient was 83. But he presented slight manifestations of cerebrospinal syphilis. *This was the only patient in the follow-up investigation whose congenital syphilis had not been cured.* But he was also the only patient who had never been re-examined after his syphilis had been treated.

Syphilis, even congenital syphilis, shows no small tendency to lapse into a latent form. The fact that a relapse may occur many years after the initial infection has induced many experts to be very reserved with regard to the prognosis and the prospects of complete recovery even when the patient is a child. SMITH has shown that the longer a group of children is kept under supervision, the greater the number of relapses. In his series of children treated with neobismuth before the age of 2 years, as many as 6 % relapsed between five and ten years after the completion of treatment. He found that 6 % relapsed when the treatment of congenital syphilis was started before the age of 3 months. Between the ages of 4 and 6 months this percentage rose to 11, between the ages of 7 and 12 months, to 15, and in the course of the second year of life, to 19. In our material there were no relapses.

LESSER was the first forcefully to advance the theory that all the alleged cases of recovery from syphilis previous to the introduction of salvarsan were in reality cases of spontaneous recovery. CASSEL was the first to record a case of spontaneous recovery from congenital syphilis, and STERN has subsequently put 6 cases on record. In our material there was 1 possible case of spontaneous recovery, though it was a case in which the infection had been weakened by anti-syphilitic treatment. This was the patient already referred to who after the completion of a course of 40 g of spirocid was still faintly Wassermann positive. At the next examination three years later, he was still faintly Wassermann-positive. The next examination, carried out 13 years



later, showed negative serological reactions in the blood and cerebrospinal fluid.

No investigation has yet been undertaken to show the extent to which congenital syphilis may end in spontaneous recovery.

BRUUSGAARD has shown in his well-known work that about 27 % of the cases of acquired syphilis end in spontaneous recovery. American experts find that this figure is applicable to congenital syphilis also. A positive Wassermann reaction due to *treponema pallidum* will in the absence of treatment always continue to be positive for at least two years, and in 90 % it will remain positive at any rate till adolescence has been reached.

The fact that congenital syphilis may relapse even after the serological reactions in the blood and cerebrospinal fluid have been negative for five years has induced American experts to demand systematic supervision for at least 10 years during which the serological reactions in the blood and cerebrospinal fluid should be negative after the completion of treatment. In this connection mention may be made of the injunction given at the present time to pregnant women who have previously suffered from syphilis always to submit to specific treatment during pregnancy even when the serological reactions have been negative for several years. This rule ought also to be applicable to pregnant women cured of congenital syphilis. But practical enforcement would raise such great difficulties that it would be seldom or never followed.

*Intelligence tests* gave the following results.

*Table VI*

I. Q.	>—85:	16	patients
»	75—85:	8	»
»	55—75:	5	»
»	35—55:	0	»
»	<—35:	1	»

O. FOURNIER, O. HEUBNER and C. HOCHSINGER were the first to draw attention to the connection between low intelligence and congenital syphilis. Several investigators have subsequently explored this problem, but with widely differing results.

The literature on the subject gives very different accounts of the number of cases of mental deficiency found among persons have suffered from congenital syphilis. When the milder forms of mental deficiency are also taken into account, quite a high percentage of psychic ailments is found. STILL puts the percentage as low as 7 and BREUER as high as 57.2, while MENNINGER found a mean of 24.5 % with diminished intelligence. Here, too, mental development was best among those who received treatment in early infancy. On the basis of a follow-up study of 250 children, E. LENSTRUP has come to the conclusion that energetic treatment cannot prevent imbecility, and he expresses doubts as to the responsibility of the syphilis itself for defective intelligence. We do not know whether it is the syphilis or the poor quality of the parent stock which is responsible for a child's defective intelligence.

The number of patients in our follow-up study is too small to justify giving our results in percentages. But it is at once noticeable that only 16 out of 30 children showed normal mental development, and only 6 showed a considerable degree of lowered intelligence. We have tried to form an estimate of the quality of the parent stock from which these children came by conversations with one or both parents, and by a perusal of the case records giving information about the parents from the time of the first admission to hospital. Among the 14 patients with an I. Q. under 85, there was only 1 in whose case record the remark was made that the parents seemed to be mentally normal. About the parents of the remaining 13 children, the following data were recorded.

*Table VII*

1. Mother backward, with low I. Q.
2. Child illegitimate, deserted by mother, put out to board.
3. Father drunkard.
4. Father drunkard, work-shy, amoral, asocial.
- \*5. Wassermann positive in the cerebrospinal fluid in infancy. Mother apparently not quite normal.
- \*6. Father drunkard, brutal, thief.
7. Father thief and Quisling.

- \*\*8. Precipitate labour. Father work-shy and drunkard.
- 9. Father drunkard. Child illegitimate. Cerebrospinal syphilis.
- \*10. Both parents drunkards. Mother and a sister without congenital syphilis debilitated.
- \*11. Both parents mentally backward.
- 12. Father and stepmother drunkards. Wretched home conditions.
- \*13. Mother mentally backward.

The 1 patient who was an idiot is indicated by \*\*. The 5 debilitated patients are indicated by \*. One of them suffered from cerebrospinal syphilis in infancy.

It is remarkable that in as many as 13 of these 14 cases with a low I. Q. one or both parents presented psychic defects. This observation does much to support the teaching *that when early congenital syphilis is given adequate treatment and the cerebrospinal fluid is normal, a low I. Q. is not due to syphilis but is the result of the hereditary influence of a parent stock of poor quality*. For the sake of comparison it may be noted that among the 16 patients with an I. Q. over 85 there were 14 about whom it was recorded that their parents were normally equipped, while the mothers of 2 of them gave the impression of mental backwardness. These two children had an I. Q. of 91.

Summarizing the results of acetarsol treatment, we find that it is potent in the treatment of syphilis, fully deserving its place as a specific remedy in infancy. It gives just as good results as other preparations, is much easier to administer, and requires shorter time. Like all other preparations, it achieves good results which are inversely proportional to the length of the interval between birth and the commencement of treatment. The serological reactions may become negative after only a few grams of spirocid, and as a rule they become permanently negative after about 40 g of spirocid, i.e. one course of treatment according to Müller's method. However, there were some cases in which one or several serological reactions were faintly positive directly after the completion of a course of treatment. But in nearly all these cases the reactions became negative a little later and without further treatment having been given. There were no definite and severe complications, and what was taken to be an acetarsol paralysis may

also have been due to syphilis. As for the 2 patients who developed spastic paresis, even if the syphilis was responsible for it, the result would have been the same with any other treatment. Fully half the number of the patients undergoing this follow-up examination were mentally normal, and most of those found to be mentally backward came of poor parent stock. Early and adequate treatment cannot prevent the development of such congenital syphilitic stigmata as Hutchinson's teeth.

The only objection which can be raised to the use of acetarsol is the one which American investigators have emphasized much — that with ambulant treatment we cannot be sure that the drug is given according to instructions. The safest course would be to keep the patient in hospital till the treatment was completed and not discharge him before the serological reactions were negative. But this procedure is impossible today because of the great shortage of hospital beds.

Of late years a new anti-syphilitic remedy has been found in penicillin, which will, perhaps, gradually supersede all the other specific remedies, including acetarsol. But penicillin is still so new and the controlled investigations of it so brief that we have continued at the Children's Department of the Rikshospital to use acetarsol. We combine it with penicillin for the present, until the results achieved by the latter in the treatment of syphilis are more certain.

### Summary

During the period 1929—1946 a total of 34 infants were treated adequately with spirocid (acetarsol) at Department of Paediatrics Rikshospitalet, Oslo. The total quantity of spirocid administered varied between 5—80 g. No definite grave complications occurred. Thirty of these infants came for control from 2 to 18 years after the treatment had been terminated. One of these had positive seroreactions and positive Wassermann's reaction in the spinal fluid. All the remaining patients were healthy except two who had been exposed to traumatic brain injury at birth and had spastic paraplegia of the lower extremities. Four of 23 possible cases had Hutchinson teeth. There were no

skull changes. The I. Q. examination demonstrated 16 patients with normal I. Q.'s, 8 who were backward, 5 who were feeble-minded and 1 idiot. Psychic defects were demonstrated in the majority of the parents of the psychically retarded children. Poor inheritance, therefore, may have been the cause of the reduced intelligence of these children with congenital syphilis. Acetarsol administered in adequate doses to infants must be regarded as an antisyphilitic as effective as other recognized agents.

### Résumé

Pendant la période 1929—1946 un total de 34 enfants ont été traités adéquatement au spirocide (acétarsol) au Service des Enfants du Rikshospital d'Oslo. La quantité totale de spirocide administrée a varié de 5 à 80 grammes. Il n'y a pas eu de complications graves précises. 30 de ces enfants sont venus au contrôle de 2 à 18 ans après la fin du traitement. L'un d'entre eux présentait des séroréactions positives et une réaction de Wassermann positive du liquide spinal. Tous les autres étaient en bonne santé, sauf deux qui à la naissance avaient été exposés à une lésion traumatique du cerveau et qui souffraient de paraplégie spasmodique des extrémités inférieures. De 23 cas possibles, 4 avaient des dents d'Hutchinson. Il n'y avait pas de modifications du crâne. L'examen du Q. I. a établi que 16 des sujets avaient un Q. I. normal, que 8 étaient arriérés, 5 faibles d'esprit et 1 idiot. On a constaté des déficiences psychiques chez la majorité des parents des enfants psychiquement arriérés. Les tares héréditaires peuvent donc avoir été la cause de l'intelligence réduite de ces enfants atteints de syphilis congénitale. L'acétarsol administré aux enfants en doses appropriées doit être considéré comme un traitement antisyphilitique aussi efficace que les autres agents reconnus.

### Zusammenfassung

In der Zeit von 1929—1946 wurden auf der pädiatrischen Abteilung des Reichshospitals in Oslo eine Anzahl von 34 Kindern in entsprechender Weise mit Spirocid (Acetarsol) behandelt. Die Gesamtmenge des angewendeten Spirocids schwankte zwi-

schen 5—80 g. Es kamen keine besonders ernste Komplikationen vor. 30 von diesen Kindern kamen 2—18 Jahre nach Abschluss der Behandlung zur Kontrolle. Eines davon hatte positive Sero-reaktion und positive Wassermann-Reaktion im Liquor spinalis. Alle übrigen Patienten waren gesund, ausgenommen 2, die infolge eines bei der Geburt erlittenen traumatischen Hirnschadens spastische Paraplegie der unteren Extremitäten aufwiesen. 4 von 23 in Frage kommenden Fällen hatten Hutchinson-Zähne. Schädelveränderungen gab es keine. Die Intelligenzprüfung ergab 16 Patienten mit normalem I-Qu, 8 Zurückgebliebene, 5 Geistes-schwache und einen Idioten. Bei den psychisch gehemmten Kindern wies die Mehrzahl der Eltern psychische Defekte auf. Bei den Kindern mit kongenitaler Syphilis scheint also minderwertige Erbanlage die Ursache der herabgesetzten Intelligenz zu sein. Acetarsol, in entsprechenden Dosen bei Kindern angewendet, muss als antisiphilitisch effektiv, als auch von anderer beachtenswerter Wirkung angesehen werden.

#### Resumen

Durante el período comprendido entre 1929 y 1946 un total de 34 niños han sido tratados adecuadamente con espirocido (acetarsol) en el Departamento de Pediatría del Rikshospital de Oslo. La cantidad total de espirocido ha variado de 5 a 80 gramos. No han podido determinarse complicaciones graves. 30 de estos niños se han presentado para comprobar su estado de 2 a 18 años después de finalizar el tratamiento. Entre ellos uno presentaba serorreacciones positivas y una reacción Wassermann del líquido espinal positiva. Todos los demás disfrutaban de buena salud, salvo dos que al nacer habían padecido una lesión traumática del cerebro y que sufrían paraplejía espasmódica de las extremidades inferiores. De 23 casos posibles, 4 tenían dientes de Hutchinson. No había modificaciones del cráneo. El examen del C. I. ha demostrado que 16 de los tratados tenían un C. I. normal, que 8 eran retrasados mentales, 5 débiles de carácter y 1 idiota. Se han comprobado deficiencias físicas en la mayoría de los padres de los niños físicamente retrasados. Las taras hereditarias pudieron haber sido la causa de la inteligencia reducida en

los casos de niños atacados de sífilis congénita. El acetarsol administrado a los niños en dosis apropiadas debe ser considerado como un tratamiento antisifilítico tan eficaz como los otros agentes conocidos.

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## **$\beta$ -Hemolytic Streptococci in the Disease Groups Eczema Infantum-Prurigo**

by

**ANJA HELVE, NILS OKER-BLOM and RISTO PÄTIÄLÄ**

The etiology of eczema infantum<sup>1</sup> and allied diseases has been studied widely and in great detail (3—10, 13, 14). Statements to the effect that it is caused by bacteria are found off and on in the literature dealing with this subject in general (18—19, 21, 24—26, 27). In a comprehensive study containing many references to the literature NORDLIND (1946) called attention to the importance of bacteria in Besnier's prurigo. It has been pointed out that an acute infection in the nose does not cause allergic asthma but increases the sensibility of the patient. These studies suggested the possibility that infantile eczema is of infectious origin, a hypothesis which has been supported by the results of treatment (1). Our favourable experience with penicillin treatment also indicated a possible infectious etiology.

For an investigation of nosocomial infections<sup>2</sup> samples for bacteriological study were taken in March—April last year (1948) from all patients' rooms in use in the Children's Clinic of the University of Helsinki. An air-sampler of Bourdillon type was used (2).  $\beta$ -hemolytic streptococci were obtained in large quantities from the rooms in which eczematous children were nursed and the total content of bacteria in these rooms was usually high.

The finding of numerous streptococci in the air of these rooms seems to support previous findings as to the role of infection in

<sup>1</sup> In the Anglo-Saxon literature this group is called atopic dermatitis.

<sup>2</sup> Unpublished work by A. HELVE.



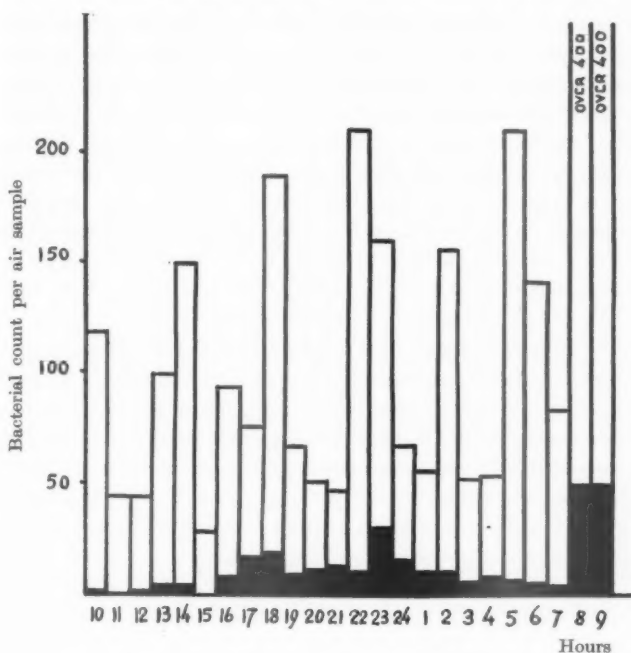


Fig. 1. Variations in total content of bacteria and number of  $\beta$ -hemolytic streptococci over 24-hour period (April 12-13, 1948) in the room of three children with eczema infantum.

- Total bacteria in 100 liters air.  
 ■  $\beta$ -hemolytic streptococci in 667 liters air.

this disease. Therefore we studied the question in greater detail by culturing samples from the pharynx, nose and skin of children so affected. We also tried to determine the extent to which antibodies were present in these children.

Samples for bacteriological study were taken from the pharynx, nose and skin of 44 eczematous children in April to Dec. 1948. Of these children 32 were under 2 and 12 over 2 years of age. For purposes of control, throat and nose swabs were also taken from 75 other children under treatment in the hospital;

they included no known case of pharyngitis but were not otherwise selected. As far as possible the control cases were of about the same age as the eczematous children studied, since it is to be expected that older children will have more antibodies; sub-clinical and mild clinical pharyngitis are particularly common in children of play and school age. The swabs from the control children were taken in Dec. 1948. As is well known, hemolytic streptococci are usually most frequent during the winter months. — Cotton swabs were used, followed immediately by culture on blood agar plates. The streptococci were not typed; they were only classified on the basis of beta hemolysis.

The antistreptolysin titer was determined in the group of eczematous children mentioned above and in addition in 24 adult cases of prurigo diathesique Besnier. In many of these patients several determinations were made and the highest figure obtained was recorded. At the same time control studies were made on 65 inmates of Children's institutions who as far as was known were free from any infectious diseases or eczemas; these children were divided into two groups of which the first included 32, ranging in age from 1 month to 2 years, and the second 33 whose ages varied from 2 to 12 years. The antistaphylolysin titer was determined in 11 of the eczematous children and in 22 of the institution children just mentioned. The antistreptolysin and antistaphylolysin titers were determined according to a method previously described (15—17, 28); it should be noted that the standard error of the AST proved to be about 30 % (OKER-BLOM, unpublished work).

Certain differences have been observed in the sugar tolerance curves between eczematous children and other children and therefore we studied this question also (20—23). Sugar tolerance tests were made on a total of 9 eczematous children and 6 adults, the blood sugar being determined according to HAGEDORN and JENSEN.

### Results

In the eczematous children culture showed hemolytic streptococci in 25 % of the nose swabs, 62.5 % of the throat swabs, and

32.5 % of the skin swabs. In these latter, hemolytic staphylococci generally grew most abundantly. From the nose swabs of the control children hemolytic streptococci were obtained in 1 case, or about 1.35 %, and from throat swabs in about 10 cases.

In Table I the nose and throat swabs are classified according to the number of colonies found (Hamburger). It shows that the noses and pharynxes of children with eczema infantum as a rule contained more streptococci than those of other children.

Table I.

Culture of streptococci from noses and throats of eczematous children.

	Nose Swabs			Throat Swabs		
	1 to 10 discrete colonies on the plate	10 to 40 colonies on the plate	Heavy growth or pure culture on the plate	1 to 10 discrete colonies on the plate	10 to 40 colonies on the plate	Heavy growth or pure culture on the plate
	+	++	+++	+	++	+++
Eczematous Children . .	10 %	15 %	0 %	17 %	20 %	25 %
Controls . . .	1 %	1 %	0 %	10 %	9 %	1 %

In 32 children with eczema infantum aged 1 month to 2 years the antistreptolysin titer was on an average 135.8. In 2 of these cases the AST was exceptionally high, in 1 of them it was 800, which was ascribed to the fact that the child had a coincidental bronchitis (29). In the other of these 2 cases the AST was 500 and the child had septicemia. In children with eczemas of prurigo type ranging in age from 3.5 to 16 years the AST was determined in only 12 cases. The average AST was 139.5. The AST was also determined in 24 adults with prurigo diathesique Besnier and it averaged 210.3. The AST of the control children was on an average 274.2. In a previous study of 100 healthy adult individuals in Finland the mean AST was 128.

Table II.

Mean antistreptolysin titers in different age groups.

Group	Number of Subjects	Antistreptolysin Titers				Mean AST
		0 to 100	101 to 200	201 to 400	401—	
Children {	Eczema Inf.	32	21	7	2	135.8
	Prurigo Type	12	7	2	3	139.5
	Control . . . .	65 { 32	14	8	7	182.5
		33	17	7	14	350.0
Adults (Prurigo) . . . . .	24	7	8	7	2	210.3

The average antistaphylolysin titer in the eczematous children was 1.17 and in the control group 0.99.

Table III.

Mean antistaphylolysin titers.

	Children with Eczema Infantum	Controls
Number of Tests . . . . .	11	22
Mean Antistaphylolysin Titer . . . . .	1.17	0.99

Two diagrams illustrate the results of the sugar tolerance tests. The first of these (Fig. 2) shows the sugar tolerance curves of 8 eczematous children at the manifest stage of the disease, and the second (Fig. 3) shows in addition those of 5 adults with manifest prurigo; the two highest curves indicate the sugar tolerances of an adult and a child suffering from Besnier's prurigo and of a child during an exacerbation of the disease, i.e. when symptoms become manifest after being latent. In the children the sugar tolerance values were generally lower at the manifest stage, as has been observed previously (23).

### Discussion

The finding of many streptococci in the air of children's wards and in the nose and throat swabs supports the observation made

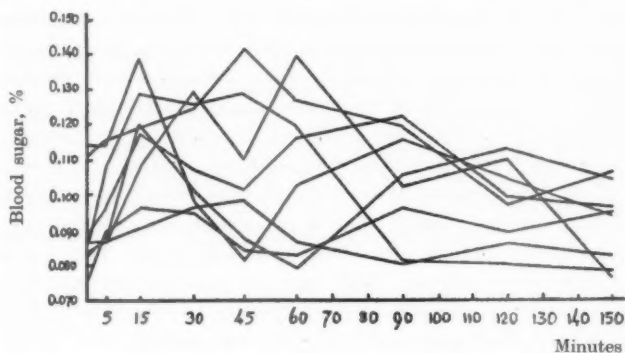


Fig. 2. Sugar tolerance curves of 8 children suffering from eczema infantum (manifest stage).

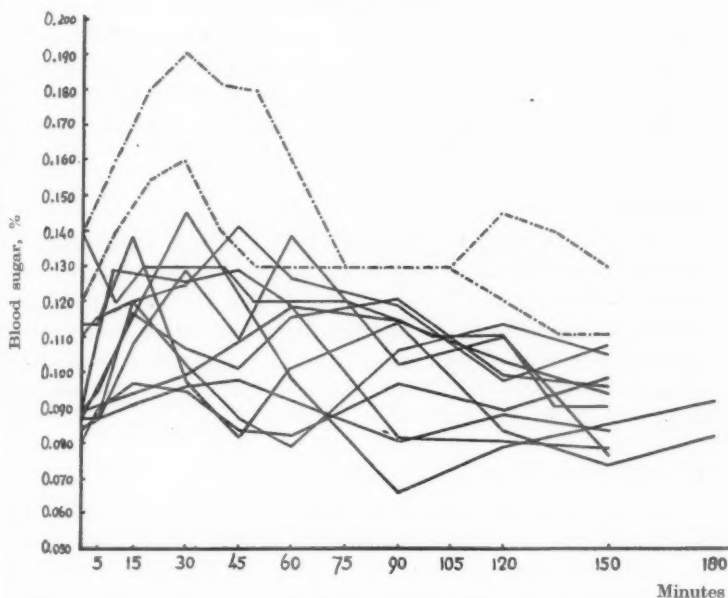


Fig. 3. Sugar tolerance curves of 8 children with eczema infantum and 5 adults with Besnier's prurigo at manifest stage of disease (—), and of 1 adult with Besnier's prurigo and 1 child during an exacerbation of the disease (---).

earlier that the etiology of eczema infantum is partially infectious. The low AST values, on the other hand, argue against a possible streptococcic-infectious etiology. No correlation was observed between the frequency of streptococci and the low AST values. It is possible that eczematous children are more apt to be carriers of streptococcic infection than other children. Practical experience has often shown that children with infantile eczema have infected their surroundings, which fact is of importance when deciding where to place nurses and children in a hospital. The changed sugar tolerance and low AST may be presumed to be closely related to the so-called exudative habitus. As far as we can see, the question here may be one of hyp immunity.

### Summary

A great number of hemolytic streptococci were found in the wards in which eczematous children were nursed in the Children's Clinic. Nose, throat and skin swabs obtained from such children of varying ages yielded numerous streptococci. The AST of these children was usually low and so were the sugar tolerance values at the manifest stage of the disease.

### Résumé

On a trouvé dans les chambres de la Clinique d'enfants où des enfants eczémateux ont été traités un grand nombre de streptocoques hémolytiques. Le nez, la gorge et les particules de peau obtenues de ces enfants, d'âges différents, renfermaient une grande quantité de streptocoques. L'AST de ces enfants était généralement bas ainsi que les valeurs de tolérance de sucre au stade manifeste de la maladie.

### Zusammenfassung

In der Abteilung für ekzematöse Kinder der Kinderklinik wurden hämolytische Streptokokken in grosser Menge gefunden. Abstriche von Nase, Rachen und Haut solcher Kinder verschiedenen Alters ergaben zahlreiche Streptokokken. Der AST dieser Kinder war allgemein niedrig und ebenso die Werte der Zuckertoleranz im manifesten Stadium der Krankheit.

## Resumen

En las habitaciones de la Clínica de Niños, donde los niños eczemosos han sido tratados, se ha encontrado un gran número de estreptococos hemolíticos. La nariz, la garganta y las partículas de la piel obtenidas de estos niños, de edades diferentes, contenían una gran cantidad de estreptococos. El AST de estos niños era generalmente bajo, así como los valores de tolerancia de azúcar, al estadio manifiesto de la enfermedad.

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FROM THE PÆDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
(FORMER CHIEF: PROFESSOR A. LICHTENSTEIN. PRESENT CHIEF: PRO-  
FESSOR C. GYLLENSWÄRD.)

## Photic Stimulation as an Aid in Electroencephalography A Report of Three Cases

By

KARL-AXEL MELIN

When a stimulus is applied to a receptor, the result is an electrical discharge in the cerebral cortex. When this stimulus is given simultaneously to a group of receptors, the response is more widespread and easier to examine. Among groups of receptors of this kind, the eye is particularly easy to stimulate. Illumination of the retina will drive a whole shower of impulses to the cerebral cortex. According to ADRIAN and MATTHEWS, the spontaneous electrical brain activity can be partly controlled by intermittent illumination of the retina. Their experiments have since been confirmed by a number of investigators. Some years ago these investigations were brought to clinical applicability (WALTER and WALTER, CORNIL, GASTAUT, GASTAUT and ROGER, MONNIER, et al.), and the method of intermittent photic stimulation has become a useful aid in the clinical EEG-laboratories. When light impulses to the retina are given intermittently, at regular intervals, some subjects will answer with synchronous brain rhythms in certain frequency bands. This is considered to be a normal response. In some epileptics, however, photic stimulation of this type will either evoke seizure discharges in the electroencephalogram, or induce clinical seizures.

The method used in the EEG-laboratory of Kronprinsessan Lovisa's Children's Hospital is similar to the one introduced by GREY WALTER. The EEG is taken bipolarly from the parieto-temporo-occipital parts of the head. Collodion electrodes are used. The EEG is recorded through five of the channels in a six-channel electroencephalograph, a Grass Model III. Channel six is coupled to a photo electric cell, placed imme-



diately by the side of the patient and registering the different light impulses. In this way, the EEG tracing can all the time in the record be compared with the intermittent light frequency.

The light impulses are produced by a high power stroboscope, manufactured by Scophony Baird Ltd. This apparatus gives flashes of blue-white light, with a time constant of 15 microseconds. The frequency can be varied from 4.5 to 25 flashes per second, without any changes in the duration or brilliance, and to 100 flashes per second at reduced intensity. The peak intensity of the flash is about 88 000 candles (all data acc. GREY WALTER). The stroboscope lamp should be fixed a few centimetres above the eyes of the subject in order to ensure as complete illumination of both eyes as possible. It has been necessary to install extra shielding with grounded wire between the patient and the electroencephalograph. It, nevertheless, still remains a problem how to get rid of artefacts in the EEG, induced from the flickering light. However, these artefacts are very easily recognized. They consist of short spikes, synchronous with the registered flashes (see Diagram IV, Fig. 4).

In the present author's EEG laboratory, the method has been adopted mainly for activation purposes on epileptic children. After the ordinary EEG examination, the patient has been placed so as to look with open eyes straight into the stroboscope lamp. In all cases, stimulation has been carried through the frequencies of 4.5 to 25 flashes per second, and under certain conditions even with different frequencies between 25 and 100 flashes per second. The smallness of the material does not justify a statistical analysis. Here, only the usefulness of the method will be discussed with a report of three cases. In one of these cases the diagnosis has been ascertained by means of this method. In the other two, valuable information has been obtained regarding the treatment.

*Case 1.* (KLB, EEG No. 1922.) A girl, aged 14. Earlier history of no particular interest. Since the age of 13, on three occasions, with long intervals between, she was found lying heavily asleep on the floor. No mention of any attack or other peculiar symptom. Examined at the KLB Out-patients' Department in October 1949. No noteworthy observations. Normal neurological examination. EEG slightly slow but without any special findings (Diagram I, Fig. 1). Renewed EEG examination a month later (Diagram I, Fig. 2) showed the same picture. Photic stimulation gave no response at slow light frequencies (Diagram

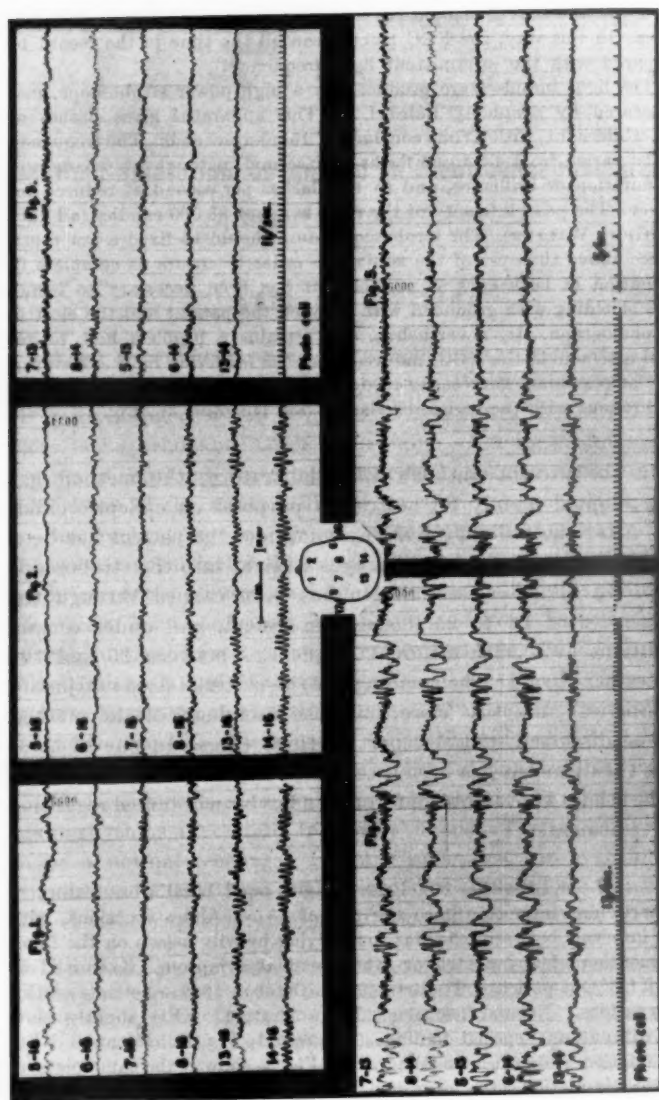


Diagram I, Case 1. For explanation, see the text. The figures on the left side of the records, in this and in the following diagrams, refer to the different electrode positions which are marked in a sketch of the head in each diagram.

I, Figs. 3 and 5). At a frequency of 13/sec, pathological waves appeared in the record (Diagram I, Fig. 4, Diagram II, Fig. 6). They always disappeared at frequencies below 10/sec, and returned each time the frequency was again raised to 13/sec. At a frequency of 52/sec, the patient got a typical grand mal attack (Diagram II, Fig. 7), followed by post-convulsive sleep (Diagram II, Fig. 8). Diphenyl-hydantoin treatment was instituted and she has since been free from these attacks.

*Summary:* A girl, aged 14, with a suspicious epilepsy, revealed through photic stimulation a typical grand mal attack, confirming the diagnosis.

*Case 2.* (KLB, EEG No. 2159.) A boy, aged 15. Previous history of no particular interest. At age of 5, 11 days after smallpox immunization, first grand mal. Many repeated attacks at varying intervals during the following two years. At age of 7, diphenylhydantoin treatment was introduced and he has been given 0.30 Gm of this preparation daily for eight years. No attacks observed. Neurological examination in December 1949 normal. EEG at that time slightly dysrhythmical (Diagram III, Fig. 1). The mother eagerly requested a reduced dosage of the medicine which, as she thought, made her boy rather dull and slow at his school work. Tentatively, for the next two months, he was given only 0.20 Gm of diphenylhydantoin daily. No attacks reported. At the mother's renewed request for a further reduction in the dosage, a new EEG was taken (in February 1950). The ordinary EEG was unchanged (Diagram III, Fig. 2). Photic stimulation at slow light frequencies gave no response in the record (Diagram III, Fig. 5). At a frequency of 11/sec, pathological waves appeared (Diagram III, Fig. 4), and at frequencies of 12/sec (Diagram III, Figs. 4 and 5) and 13/sec (Diagram III, Fig. 3), the patient was subjected to clinical attacks with loss of consciousness and clonic convulsions in the arms and legs. These symptoms immediately disappeared at lower or faster frequencies, and could be repeatedly induced when frequencies of 12/sec or 13/sec were used (Diagram III, Fig. 3). The examination was repeated eight times in all, each time with exactly the same result.

*Summary:* A boy, aged 15, who at the age of 5 was subjected to what was probably a vaccination encephalitis, followed by grand mal epilepsy. The reduction, or discontinuation, of the treatment was considered. EEG was pathological and photic stimulation induced series of minor seizures. Discontinuation of the treatment was out of the question.

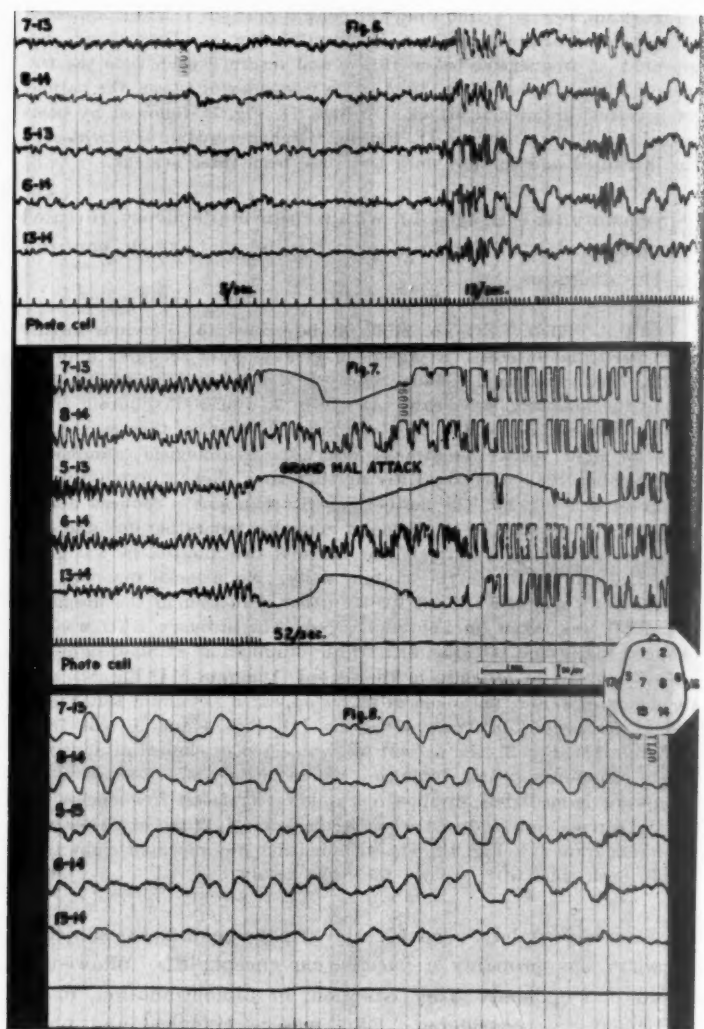


Diagram II. Case I. (Continued.) For explanation, see the text.

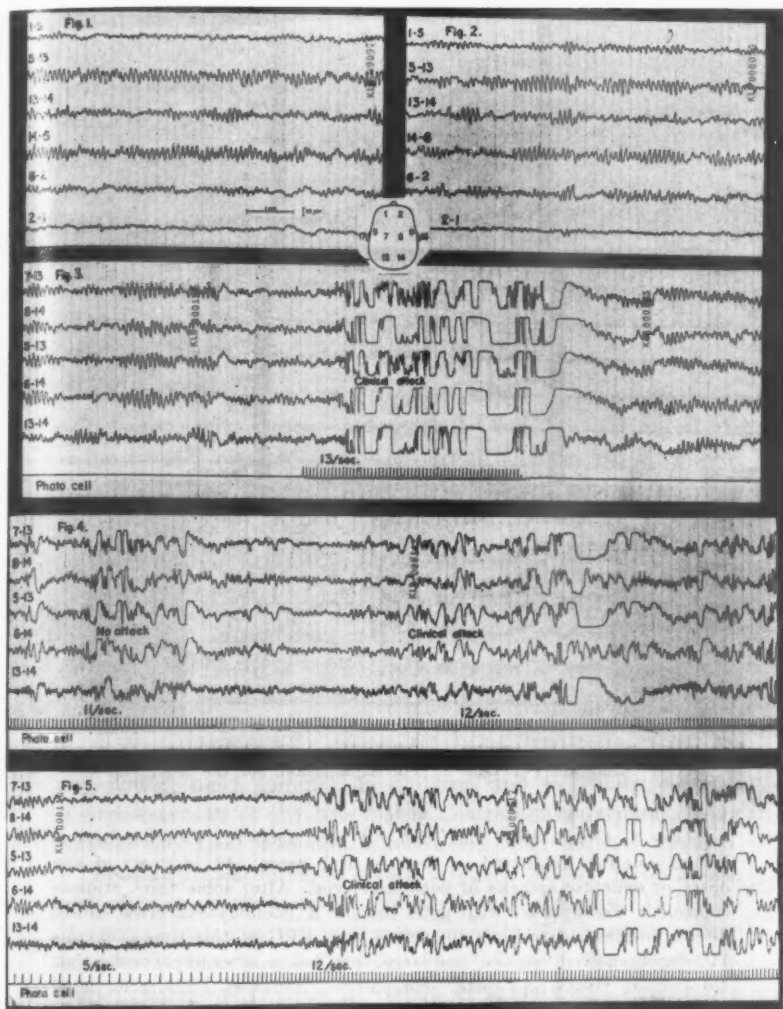


Diagram III. Case 2. For explanation, see the text.

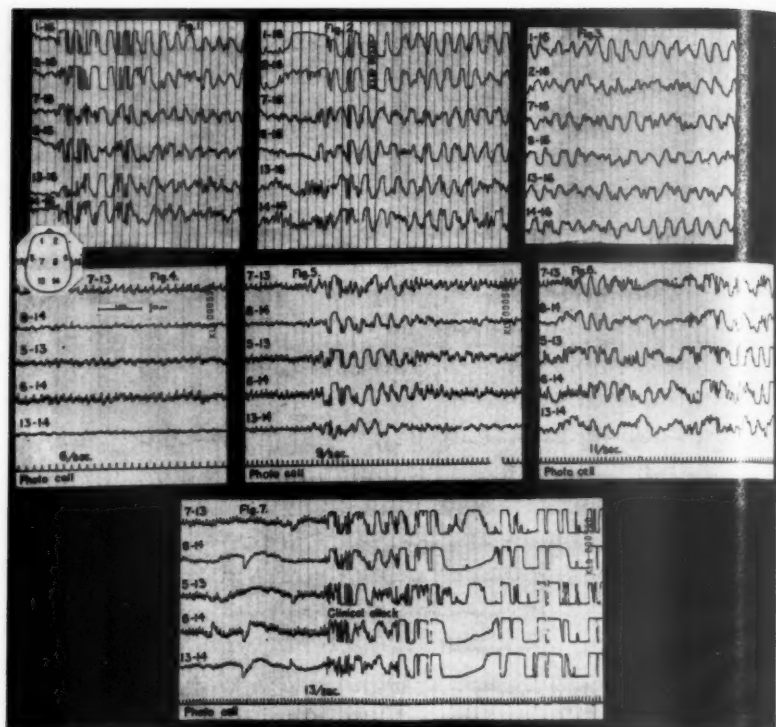


Diagram IV. Case 3. For explanation, see the text.

*Case 3.* (KLB, EEG No. 1695.) A boy, aged 12. Familiar haemolytical jaundice diagnosed at the age of 7 years. At 11 years of age, onset of epileptic attacks of petit mal type. After some time, tridione treatment was applied with good result. A haemolytical crisis caused discontinuation of tridione treatment. An EEG at this time (Diagram IV, Fig. 1) showed "spikes" and large, slow waves, after hyperventilation. No typical "wave-and-spike" complexes. Renewed EEG, a fortnight later, after new tridione treatment for some days, showed almost the same picture (Diagram IV, Fig. 2). Shortly afterwards, he was free from petit mal attacks. Five months later, in the hospital for control examination. The father wanted the treatment to be discontinued.

Renewed EEG examination revealed a normal EEG. Hyperventilation gave a moderate build-up (Diagram IV, Fig. 3), but no "spikes" or "spike-and-wave" complexes. Photic stimulation at slow frequencies gave no response (Diagram IV, Fig. 4). At a light frequency of 9/sec, pathological waves appeared (Diagram IV, Fig. 5). At 11/sec, the record consisted chiefly of pathological waves (Diagram IV, Fig. 6), and at 13/sec (Diagram IV, Fig. 7) a clinical attack started, mainly of the type of a long absence with slight myoclonic jerking.

*Summary:* A boy, aged 12, with petit mal epilepsy since the age of 7. Free from seizures after tridione treatment. The father requested the treatment to be discontinued, but an EEG examination revealed, by means of photic stimulation, a clinical attack. Tridione treatment had to be kept up.

In the literature on this subject, 4 to 8 % of epileptics are said to respond to photic stimulation, clinically as induced attacks, or only electroencephalographically, as seizure discharges in the record. GASTAUT, ROGER and GASTAUT, who possess extensive experience in this field, obtained their responses mainly at an illumination frequency of 10—20 flashes per second, in most cases at 12—16. In their collected material, 4 % of the epileptics showed changes provoked by the stroboscopic method. However, the information gained is of such considerable value that, in spite of the low frequency of positive tests, the method should be included in the routine procedures of the clinical EEG laboratories. This is particularly important in laboratories for children. The "photogenic" epilepsy discussed here is, without any doubt, most common in children and in young persons. (Comp. GASTAUT et al.) The test is also rather convenient, being without any risk of complications other than induced seizures.

Photic stimulation is, as shown in Case 1, an aid in obtaining correct diagnosis in some uncertain cases of epilepsy. It is also of decisive value in the treatment control. The present author has several times pointed out the onesidedness in the use of electroencephalography. It is, no doubt, of considerable significance as a diagnostic method in many different conditions. The importance of observing the patients, the course of their healing, and the effect of the treatment has been more or less forgotten in



many EEG centres. Repeated examinations are essential, not least in the various types of seizure diseases treated with any of the numerous antiepileptic remedies of our time. As shown in Cases 2 and 3, photic stimulation offers new possibilities of increasing the accuracy of examination. As GASTAUT and his co-workers emphasized, regular EEG control, including photic stimulation, is of the utmost importance, in view of the fact that patients sometimes appear to be clinically cured though they continue to disclose EEG anomalies that contraindicate interrupted treatment.

### Summary

Three cases of epilepsy are reported, all examined by means of electroencephalography and photic stimulation. This activation method increases the accuracy of the EEG examination, and 4 to 8 % of the epileptics react positively. During the EEG examinations, the eyes are illuminated from a stroboscope with a lamp emitting very short, brilliant light impulses of different frequencies. Many normal subjects respond to the intermittent light impulses at certain frequencies with synchronous brain rhythms. Some epileptics will be subjected to seizure discharges in the EEG at certain light frequencies, or the patient will have clinical seizures.

This was the matter in the three cases described.

### Résumé

On rapporte trois cas d'épilepsie, qui ont tous été examinés à l'aide de l'électro-encéphalographie et de la stimulation lumineuse. Cette méthode d'activation augmente la précision de l'examen EEG et 4 à 8 % des épileptiques réagissent positivement. Pendant les examens EEG, les yeux sont illuminés par un stroboscope avec une lampe émettant des impulsions très brèves de forte lumière de différentes fréquences. Beaucoup de sujet normaux répondent à la stimulation intermittente de lumière à certaines fréquences par des rythmes synchroniques du cerveau. Certains épileptiques seront soumis à des ondes patho-



logiques dans EEG à certaines fréquences lumineuses, ou le sujet aura des chocs cliniques.

Cela a été le cas chez les trois sujets examinés.

### **Zusammenfassung**

Drei Fälle von Epilepsie werden mitgeteilt, welche elektroencephalografisch mit Lichtstimulation untersucht wurden. Diese Methode, auf welche 4—8 % der Epilepsiefälle positiv reagieren, steigert den Wert der EEG-Untersuchung. Die Augen werden vermittelst eines Stroboscopes mit einer Lampe, die sehr kurze scharfe Lichtimpulsen mit wechselnder Frequenz aussendet, beleuchtet. Viele normale Personen reagieren auf die intermittenten Lichtimpulse mit gewissen Frequenzen mit synkronen Gehirnwellen. Gewisse Epileptiker zeigen bei bestimmten Lichtfrequenzen EEG-Veränderungen. In einige Fälle wird auch ein klinischer Anfall ausgelöst, so in sämtlichen drei mitgeteilten Fällen.

### **Resumen**

Nos presenta tres casos de epilepsia, los cuales han sido examinados con ayuda de la electroencefalografía y de estímulos fóticos. Este método de activar aumenta la precisión del examen EEG y de 4 a 8 % de los epilépticos reaccionan positivamente. Durante los exámenes EEG, los ojos se iluminan por un estroboscopio con una lámpara que emite impulsiones muy cortas de luz fuerte de diferentes frecuencias. Muchos de los sujetos normales responden a las impulsiones intermitentes de luz a ciertas frecuencias con ritmos sincrónicos del cerebro. Algunos epilépticos serán sometidos a ondas patológicas en EEG a ciertas frecuencias luminosas o el individuo tendrá choques clínicos.

Este ha sido el caso en los tres individuos examinados.

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## CASE REPORTS

### A Case of Progeronanism (Progeria of Gilford)

by

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As an anatomical examination of the patient who was described by SCHIPPERS in 1916 and who died in 1939 was possible, and as we also possess ample clinical data on the further life of the patient, we feel justified in recording the following information.

X. was the first child of healthy parents. There was nothing special in the family history. The child was born spontaneously and at term. The birthweight was 2750 g. Even during the first year the parents observed the large skull with the prominent veins. After the first year the hair became white and fell out. At the age of 1½ years the first teeth became visible and the patient learned to walk; at the age of 2 years he started to talk. At the age of 3½ he was taken into the Emma Childrens' Hospital at Amsterdam. His length was 84 cm (normal: 96 cm) and his weight 11.3 kg (normal: 15.6 kg). His brow was peculiarly large and round; the nose bone was deeply sunk. The eyes protruded; there were no eyebrows and hardly any lashes. The facial expression was oldish. The veins on skull and forehead were prominent. The skin of the skull was atrophic and was covered by sparse, thin and faded hairs. The large fontanel was open. The skin of trunk and limbs was dry and wrinkled and irregularly pigmented; it resembled that of an old man. Trunk and limbs were slender and well proportioned. The joints (especially those of the knees) were prominent. The nails of the toes showed onychogryposis. Internal and neurologic examination did not reveal any abnormalities. With regard to age the ossification of the carpus was normal.

At the age of 10 years the hands showed the typical aspect of those of an old man with trophic disturbances of the nails. The pigmentation of the skin had increased. The patient suffered much from cold and heat. His intellect was very good and he was at the head of his class.

<sup>1</sup> This paper was written in 1940. Due to war and post-war circumstances it could not be published until now. The author did not have the opportunity to refer to the literature since 1940.



Fig. 1. Patient X ( $13\frac{1}{2}$  years old).

At the age of  $12\frac{1}{2}$  his blood pressure was 110/85. The second aorta tone was too loud. At 16 he suffered a luxation of the hip. At 18 the blood pressure had mounted to 132/90. The pigmentation of the skin had become very intensive. Cardiac murmurs were audible at all valves.

Thereafter the patient was lost from sight until he was admitted to the municipal hospital at Zaandam (Dr. W. H. Beekhuis) at the age of 26. His personal history revealed that every evening he was very short of breath and also after slight effort in the daytime. One month before his admission to the hospital he suffered an attack of cardiac asthma. His profession was instructor in Esperanto. His family doctor stated that he was very intelligent. On examination it appeared that his nutritional condition was bad. He showed signs of cyanosis, but none of oedema or jaundice. His length was 115 cm, his weight 15.5 kg. The skull was large with a maximal perimeter of 52.5 cm. The face was very small, with a long, narrow, hooked nose, exophthalmos and pronounced atrophy of the jaws. The teeth were carious. There were no eyebrows, sparse greyish lashes and no axillary, pubic or other hair. The skin was dry, scaly, wrinkled and pigmented and there seemed to be a total lack of all subcutaneous fat. The thorax was conical, with a narrow upper aperture. The clavicles were small. The joints were very prominent, especially those of the knees and elbows. The fingers and toes were clumsy and short; the nails were small and crumbling. Internal examination revealed loud systolic and diastolic heart murmurs. The blood-pressure was 180/120. The liver was enlarged and reached as far as two fingers below the ribbow. The size of the genitals was normal and



Fig. 2. Patient X (25 years old).

the testicles were well developed. The tendon reflexes were low; pathological reflexes did not occur.

**Biochemical Examination:** Urine: albumen +, sugar—, urobilin +, many leukocytes and some cylinders. Rowntree test: within two hours 37 % (normal 60 %). Van Slyke test: standard clearance 14 (= 26 % functional renal tissue). Faeces: benzidine test: —. Blood: ureum contents 650 mg/l and 310 mg/l; calcium 10.6 mg/100 cc serum; anorganic phosphor 4.0 mg/100 cc serum; blood sugar before use of 20 g glucose: I. 17 %; one half hour after use: I. 95 %, one hour after: 1.80 %, one and one half hours after: 1.86 %, two hours after: 1.25 %, two and one half hours after: 1.23 %. Basal metabolism: 114 %.

**Electrocardiogram:** alterations, indicating a degeneration of the myocard, with the possibility of a healed myocard infarct.

X-ray examination: heart dilated to the right. The skeleton gave the impression of being that of a seven or eight year old child. The thoracic vertebrae were convex at the upper and lower sides. The skeleton revealed a lack of calcium, especially in the crests of the pelvis where the structure was totally missing at many places. The ribs also showed the same structure; at some spots they looked «moth-eaten»; sometimes they resembled a beginning cystic formation. The left eighth rib showed the remainder of an old fracture. The caputs of the femur on both sides were insufficiently developed; on the left one there was hardly any caput visible on the broad collum; on the right one a forward luxation could be observed. The end phalanges of all fingers were barely developed; apparently both the diaphysis and the distal epiphysis were missing. The skull showed distinct impressioes digitatae. The base of the cranium was too short; the sella turcica had a normal form. The sphenoidal sinus and the etmoidal sinus were invisible on the x-ray picture. The skeleton of the face was very small in comparison to that of the cranium; it looked as if it was hiding underneath the anterior cranial cavity.

After a year and a half the patient again was admitted to the hospital at Zaandam. He was so short of breath that any detailed examination was impossible. He was very cyanotic and showed intensive oedema. He died the day after admission.

*Obduction report (shortened):*

The obduction took place six and one half hours post mortem. The skin was very thin and atrophic. The subcutaneous fat was at most 1 mm thick and at most places macroscopically invisible. The pleural cavities at both sides contained 40 cc of clear liquid; there were no adhesions. The pericardium contained 25 cc of clear liquid. The heart weighed 220 g and was larger than a fist; it was bluntly conical. The coronary arteries had changed into calcified tubes which were not completely closed at any point. In the front wall of the heart an old infarct was found. The trabeculae were flattened out. The chordae tendineae of the mitral valves were thickened and shrivelled; the valves themselves were also shrivelled and stiff. Yellow knobbish thickenings were found at the streamside of the valves near the thickened closing rim. In the ostium there was no room for two fingers. The aortic valves were also thickened and stiff, with masses of calcium between and on the surface of the valves, especially at the entrance of the sinus Valsalvae into the aortic wall. The aortic arch showed many thickenings of the intima and atheromatic ulcers, fatty degeneration and calcification of the intima. The lungs showed oedema. The thyroid gland was of normal size and consistency. The spleen was congested and revealed marked cartilaginous perisplenitis. The liver was also heavily congested. The adrenal glands

had a diameter of nearly 25 mm; in a cross section the cortex appeared to be very thin. The surface of the kidneys showed a small granulation with many retracted dark coloured scars and distinct stellulae Verheynei. In cross section the cortex was somewhat too narrow, with a rather clear design. In the right kidney many large cavities were found. The pelvis of this kidney was thickened and it contained three brittle brown stones. The arteries of the abdomen, the pelvis and the limbs showed distinct sclerotic degeneration. The right femur was taken out; it was heavily curved. The caput of the femur was covered with patches of cartilage, the cortex was very thin, and the medulla was as soft as a honeycomb.

The cranium was very thin, without layer structure. Externally the brains showed no abnormalities except for slight atrophy. There was only slight evidence of arteriosclerotic degeneration at the circulus arteriosus Willisii. The weight of the brains was 1 475 g, that of the pituitary gland 400 mg. Macroscopic examination showed that the latter was perfectly normal.

The microscopic examination of the lungs, the liver, the spleen and the kidneys revealed venous congestion. In the lungs emphysema was found. Incipient cirrhosis of Laennec was observed in the liver, and besides many cysts arteriosclerosis was seen in the kidneys. Microscopically the parenchymatous tissue of the internal organs showed no atrophy. In nearly all organs sclerosis of the larger and smaller arteries was found. There was extensive proliferation of connective tissue in the lymphatic glands of the neck. The thyroid showed a reduced functioning indicated by old, dark coloured colloid, hyalinization of the stroma and atrophic conditions of the follicles. The parathyroid glands were far too small and showed considerable proliferation of connective tissue. Only two of them contained groups of oxyphile cells. In the with the help of a microscope discovered remainders of the thymus only calcified, but no normal Hassal bodies existed. The pancreas showed a normal structure of the glandular tissue; the connective tissue around the ducts had proliferated. The capsule of the adrenal glands had thickened; there was no proliferation of connective tissue in the glands themselves. Local hyperplasia was visible in the center of the medulla. The insufficient development of the zona glomerulosa was very obvious in the cortex; as a whole the cortex had developed less than normal. The testes contained all stages of a normal spermatogenesis; the sperm ducts, however, contained perhaps less spermatozoon than usual. With Sudan staining many groups of interstitial cells were visible.

The anterior lobe of the pituitary gland was examined by counting the different kinds of cells according to the method indicated by RASMUSSEN. A striking deficiency in eosinophilic cells could be proved. The average percentage is 34.8 %, Rasmussen gives a minimum figure

of 22.6 %, but we found only 16.3 %! Our figures were obtained after we had practiced Rasmussen's method on 10 other pituitary glands. In the case of our patient we found the following: eosinophilic cells 16.3 %, basophilic cells 16.8 %, chromophobe cells 66.9 %. A slight proliferation of connective tissue with formation of new vessels was found in the anterior lobe. The posterior lobe showed no abnormalities.

Prof. B. BROUWER, M. D., was kind enough to perform the anatomic examination of the brains of our patient. He found arteriosclerosis of the large arteries only; the small arteries of the brains were normal. He found also senile alterations in the choroid plexus and dilatation of the infundibulum of unknown aetiology. This dilatation had caused a change in the shape of the tuber cinereum, but the hypothalamic nuclei were clearly visible and showed no abnormalities. The conclusion was made that the senile alterations in the mesodermal tissue had not caused degenerative changes in the cells of the cortex of the brains. Anatomic examination of the brains revealed no alterations which could explain the disturbance in the growth of the patient.

An anatomic examination has been made in only 2 other cases. The first obduction was GILFORD's. He did not investigate the pituitary gland, however. A second post mortem examination is described by ORRICO and STRADA. «Unimportant» changes were found in the pituitary gland and the epiphysis. They described a large cyst in the intermedial part of the pituitary gland, however!

Progeronanism cannot be regarded as the consequence of a shortage of eosinophilic cells in the pituitary gland only. Many symptoms, for instance the premature arteriosclerosis and the atrophy of the subcutaneous connective tissue, fat tissue and skeleton, cannot be explained by this shortage. There is also the insufficient development of the ligaments proved by the fact that many patients suffer a congenital luxation of the hip. The explanation of the regressive changes in all these tissues is to be found in inadequate development of the mesenchyme, that is the embryonal tissue from which have to develop the connective tissue, the cartilage and the bone tissue. Fat tissue is a special form of connective tissue and so are the tendons, the articular ligaments and the corium. The blood vessels also develop from the mesenchyme.

If we accept the theory that progeronanism is the result of a combination of pituitary dwarfism and inadequate development of all the tissue originating from the mesenchyme, then we are able to explain all the symptoms of progeronanism.

Another argument for this conception is the occurrence of sclerodermy in patients with progeronanism. (STRUNZ, POPEK and HADLIK, ZEDER.) VON BERMUTH declared that sclerodermy was a systemic disease of the mesenchyme. He described a patient with sclerodermy who afterwards suffered from univeral calcinosis, a combination also mentioned by

many other authors. VERSÉ saw a patient with universal calinosis combined with extensive calcification of the arteries. IFF described a case of congenital calcification of the large blood vessels which he considered due to insufficient development of the tissues originating from the mesenchyme. SCHULZ found extensive calcification of the large blood vessels in a child with marblebones disease; the latter disease was also explained as a disturbance in the development of the mesenchymal tissue (COHN, DRUKKER).

Thus we know a group of rare diseases which can occur simultaneously and all of which are explained as due to disturbances in the development of mesenchymal tissue. If this explanation is acceptable, we can explain the combined occurrence of premature calcification of the arteries, atrophy of the different kinds of mesenchymal tissues, and scleroderma in progeronanism.

### Summary

The author gives further clinical description and a report of anatomic investigation of a case of progeronanism, already described by SCHIPPERS in 1916. The anterior lobe of the pituitary gland proved to be deficient in eosinophilic cells. This deficiency was demonstrated objectively by the method indicated by RASMUSSEN. Progeronanism should be regarded as a particular form of pituitary dwarfism combined with inadequate development of tissue derived from the mesenchyme.

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## Severe Hypoproteinemia, Probably Caused by Hepatic Damage

by

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In recent years a clinical picture has been described the sole symptom of which is edema due to hypoproteinemia. In the available literature there are reports on 6 cases in adults (BINGER and KEITH, COPE and GOADBY, JOHANSEN, MYERS and TAYLOR, RYTAND) and 3 in children (SALOMONSEN, SCHICK and GREENBAUM, THOMPSON and MCQUARRIE). Beyond hypoproteinemia and edema no changes have been demonstrable during life, and certain authors have therefore spoken of "idiopathic hypoproteinemia." The diet has been rich in protein and Vitamin B. There has been no demonstrable disturbance of the absorptive capacity of the intestinal canal nor any pathological excretion of proteins through the urine due to renal damage or through the bowel due to chronic intestinal ulcer. There has been no anemia nor increased breaking down of the proteins due to malignant growth with cachexia. It has therefore been assumed that the cause of the hypoproteinemia was a deficiency in the production of the blood proteins. We do not know with certainty where the synthesis of the proteins takes place but the liver is probably of great importance. In these cases of hypoproteinemia, however, there has been an absence of clinically demonstrable hepatic damage, except in 1 case which showed slight changes only (MYERS and TAYLOR). The majority of the cases have recovered, sometimes after several relapses. THOMPSON and MCQUARRIE reported a case with a fatal course in a boy 2 years of age. Clinically there was no evidence of hepatic damage and macroscopically the liver appeared normal but microscopic examination revealed atrophy of the cells in the peripheral portion of the lobules.

A somewhat different picture was reported by ØDEGÅRD (2 cases) and JONES (1 case). These patients were children 3 months old who in addition to hypoproteinemia and edema also had anemia. Rh-isoimmunization could be excluded. The course of disease was fatal and in all cases autopsy revealed pronounced fatty degeneration of the liver and fibrosis of the pancreas. The combination of severe pancreatic fibrosis

and interstitial liver damage is found in a case described by BINGER and KEITH. The patient was a 62 year old man, who showed edema caused by hypoproteinemia but who also had severe steatorrhea. In each of these cases there was in all probability a lowered intestinal absorption present which at least partially caused the hypoproteinemia. The changes of the liver were possibly merely secondary, due to the disturbance of the protein absorption.

MESSINGER has described a 27 year old woman with a picture typical of "idiopathic hypoproteinemia" but with an eosinophilia of 10 %. She recovered during pregnancy and remained free from symptoms after parturition. Pregnancy has been considered to dispose towards hypoproteinemia owing to the increase in albumin requirement, and it is therefore difficult to explain the recovery if it is assumed that hepatic damage was present. Messinger considers that there was probably a decreased function of the anterior lobe of the pituitary gland which was compensated for by the pregnancy.

The etiology of these "idiopathic hypoproteinemias" is probably extremely diverse, but it is suggested that hepatic damage be suspected first even though no disturbance of hepatic function may be demonstrable either clinically or on the basis of laboratory data. This conclusion is substantiated by the following case.

#### *Case History*

Patient boy, youngest of three siblings, born on Feb. 22, 1947. Family healthy. Birth weight 3 570 g. Normal delivery. Breastfed until 8 months of age, thereafter given entirely normal diet with adequate protein and Vitamin B content. His mental and physical development were normal and previous to this illness he was in good health. On Sept. 26, 1948 (at the age of 18 months), he seemed tired and had a slight rise in temperature (38.4° C). At this time a slight swelling of the face and legs was noticed. The next day he was afebrile but became increasingly apathetic and the swelling increased. On the Oct. 5, 1948, he was admitted to the local hospital, where he was found to present a typically nephrotic appearance with the edema most pronounced in the lower legs. Proteinuria was not demonstrable, however. He had loose mucous stools up to seven times a day. On Oct. 11, 1948, he was transferred to the Norrull's Hospital.

*Condition on Admission.* — Normally developed boy, lying rather apathetically in bed. Lowered muscle tone. Edema of legs, lower portion of trunk and arms, but not of face. Pulse rate 95. Temperature 37.2° C. Heart and lungs normal. Blood pressure 100/60. Abdomen distended but no demonstrable ascites. Spleen and liver not palpable. Rectal examination normal. No neurological changes. Fundi normal.

*Laboratory Data.* — *Urine:* albumin: nil; glucose: nil; sediment: nil; bilirubin: nil; diastase (Wohlgemuth's method) 38/30 min. = 16.

*Blood:* hgb 11.6 g %; red cells  $3.53 \times 10^6$ ; hematocrit 31.5; reticulocytes 1 %; white cells 10,200. Differential count: staff cells 13 %; segmented cells 72 %; lymphocytes 10 %; eosinophiles 0; monocytes 5 %. Thrombocytes 114,000. Mean red cell diameter  $7.1 \mu$  with normal distribution. MSR 20 mm. WR neg. Antistreptolysin titer 20 units. N. P. N. 28 mg%. Electrophoretic analysis of serum: (total protein [Kjeldahl's method] 3.1 %); albumin 30.9 %; globulin  $\alpha$  12.8 %;  $\beta$  42.8 %;  $\gamma$  13.5 %. Fibrinogen 0.29 %. Blood glucose 93 mg%. Serum calcium 8.1 mg%. Serum sodium 326 mg%; serum potassium 17.1 mg%; serum chlorides 390 mg%; total serum cholesterol 182 mg%; serum bilirubin 0.3 mg%; serum phosphatase 4.2 units. Prothrombin index 86. Thymol reaction 1 unit. Takata's reaction neg. Tibial puncture showed normal bone marrow.

*Feces:* brown color, semisolid consistency. Selm + +, Katalas + +, Weber neg. No muscle fibers. No iodophile substance. No parasite eggs. Fat determination: total fat 25.43 % (free fatty acids 14.60 %, neutral fat 63.78 %, soaps 21.62 %). Dry substances in feces 19.20 %. Bacteriologic cultures showed no pathological flora.

Cultures from nose and throat were negative for diphtheria and hemolytic streptococci. Mantoux up to 1 mg was negative.

Determination of aminoacids in the blood before and after the oral administration of gelatine according to the method of Howard and Hesselvik showed a normal curve indicating a good digestion and absorption of proteins.

*X-ray* of heart and lungs gave normal findings. The liver was rather large. The skeletal system showed no pathological changes and the development of the ossification centers was normal. Electrocardiographic findings normal.

During the continued observation there was never albuminuria and the sediment was normal. There was occasionally urobilin in the urine but on no occasion was bilirubin found. Nonprotein nitrogen was normal throughout. The specific gravity of the urine varied between 1.003 and 1.024. The serum protein was consistently low. In 42 determinations the total protein varied between 2.6 % and 4.8 %, and in 42 fractional protein determinations the albumin varied between 0.6 % and 2.0 % and the globulin between 1.3 % and 3.5 %. During the first weeks there was moderate elevation of the S.R. but it subsequently became normal. At no time was there anemia.

*Course of Disease.* — During the first few days after admission the patient was apathetic, tired and distressed by vomiting. His condition soon improved, however. He became alert and interested in his surroundings, laughed and played. His stools were at times loose and frequent

but between these periods they were entirely normal and at no time bulky or fatty. The edema varied considerably, being entirely absent on several occasions. The weight varied as much as 1 kg in 24 hours. There were sometimes definite signs of ascites. The liver, which was not palpable on admission, later became markedly enlarged and reached 3 to 4 cm below the costal margin. The liver edge felt firm but smooth. The spleen was never palpable. The patient was afebrile.

He was treated with a high protein diet. On Oct. thirteenth and fourteenth he was given a plasma transfusion, followed by intravenous aminoacids and glucose for four days. Previously 300 ml Dextran was also administered. Aminoacids were given orally. Vitamin B in large doses and liver extracts were administered parenterally. There was no improvement after this treatment.

In the beginning of December there was again deterioration of the patient's condition. The stools became loose and frequent. On December thirteenth tetany occurred. The blood calcium was then 7.6 mg% and ECG showed a prolonged Q—T phase. After administration of calcium the symptoms receded rapidly but patient's general condition deteriorated and he died on Dec. seventeenth.

*Autopsy.* — The only organ that showed any changes of importance was the liver. It appeared to have increased somewhat in size. The surface was smooth. The parenchyma was markedly pale. The consistency was firm and resilient. On incision it seemed to be rather tougher than the normal. The cut surface was grey and homogeneous, without degenerative foci. The microscopic picture showed a moderate increase in the periportal connective tissue, which contained occasional fibroblasts and was infiltrated with lymphocytes, plasma cells and occasional leucocytes. The columns of cells were rather narrow and separated by wide capillaries. The hepatic cells were light in colour, with granular cytoplasm and normal nuclei. The section showed moderate, diffuse fatty degeneration, mainly with large droplets.

*Discussion.* — The essential clinical finding in this patient was a pronounced hypoproteinemia which, due to the low colloid osmotic pressure, resulted in the development of edema. The patient had always received adequate nutrition with a satisfactory content of proteins and Vitamin B. The administration of large amounts of proteins during the period of hospitalization proved to be without effect. There was no reason to assume the presence of a lowered power of absorption. Diarrhea occurred periodically, it is true, but was in all probability secondary and caused by edema of the intestinal wall. Besides, tolerance tests with casein showed satisfactory absorption. No form of abnormal breaking down or excretion of proteins was present. Protein was on no occasion demonstrable in the urine. In the presence of an increased excretion of protein there is mainly a loss of albumin with resultant hypoalbumine-

nia. In the cases of "idiopathic hypoproteinemia" described earlier the albumin-globulin ratio has commonly been normal or the albumin fraction decreased. In the present case it was rather low, though not as low as it frequently is in lipoid nephrosis. The electrophoretic analysis also failed to show as great an increase in this  $\alpha$ -component as in nephrosis and the absence of lipemia contradicts this diagnosis.

The severe hypoproteinemia can be explained only as the result of a deficiency in the production of protein. Hepatic damage was suspected in the first place, but clinically there was not much evidence supporting this diagnosis. It is true that the liver was slightly enlarged but there was no demonstrable disturbance of liver function. Serum bilirubin, the serum phosphatase, thymol reaction, Takata's reaction, total serum cholesterol and the blood corpuscle diameter all showed normal values. There was merely a slight increase in the urobilin excretion in the urine on a few occasions. As it has been held that the production of proteins also takes place in the bone marrow, a sternal puncture was carried out, but it showed a normal marrow, and roentgenographic examination of the skeleton did not establish any changes. Thus clinically there was merely a suspicion of hepatic damage. Not until the case came to autopsy was the suspicion verified. Macroscopically the liver showed but slight changes but the histological picture was clearly pathological. The cellular pattern was fairly normal. There was moderate fatty degeneration. The changes were mainly between the lobules, where there was observed an infiltration of lymphocytes, plasma cells and leukocytes, with an increase of connective tissue.

The liver is generally considered to be of great importance in the synthesis of the blood proteins, and it therefore seems justifiable to interpret the entire disease process as the result of hepatic damage. It is, however, conceivable that the hepatic damage occurred secondarily and that both the hypoproteinemia and the hepatic changes were symptoms caused by some unknown disturbance of the protein metabolism. But it is noteworthy that the case described by THOMPSON and MCQUARRIE showed a picture that clinically as well as pathologico-anatomically was in close agreement with the present case. This supports the assumption that there is a connection between this type of hypoproteinemia and hepatic damage. Whether or not the hepatic damage is primary, however, cannot be determined with certainty.

### Summary

A case of hypoproteinemia with severe edema is described, probably as the result of disturbed protein syntheses. Histology showed interstitial fibrosis of the liver.

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## **Tetanus and Atelectasis of the Lung Due to Aspiration of Garden Soil in a Boy of 17 Months**

by

**OLE CHRISTENSEN**

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Chief: VALDEMAR POULSEN, M. D.*

In a good many cases of tetanus in childhood no external injury can be demonstrated as the portal of entry for the infection. Two series of 70 and 28 patients reported by Silverthorne and Dietrich, respectively, include 15 and 13 cryptogenetic cases of this kind.

The case record published below is quite suitable for calling attention to the significance of the air passages as portals of entry for the tetanus infection in those cases where no external injury can be demonstrated.

### **Case Record (No. 674, 1947)**

The patient was a boy 17 months old with a past history of good health who was admitted to this hospital on July 2, 1947.

Eleven days before admission he became acutely ill, with a temperature of 39° C., cough and dyspnea. On the day of admission left pleurisy was diagnosed.

*Status on Admission.* Temperature 38° C. The patient was exhausted, greyish pale, moaning, with accelerated shallow breathing and distention of the alae nasi.

Inspection of the throat was very difficult because he resisted violently, but there appeared merely to be a little redness. Slightly enlarged lymph nodes were palpable at the angles of the mandible.



Fig. 1.

Auscultation of the lungs shows marked dullness and impaired respiration over the entire left lung. Heart sounds normal. Abdomen and extremities: no abnormalities.

Pleural puncture yielded a little mucoid, blood-tinged fluid which gave no bacterial growth in cultures on agar and broth.

*Roentgenography of the Chest, July 3, 1947 (Fig. 1).*

The heart was pulled entirely over in the left side of the chest, where the shadow was perhaps a little less dense along the wall. Presumably this was a case of complete atelectasis of the left lung, with displacement of the heart (signed H. Christiansen).

The patient was given alfasol 35 cg  $\times$  6, and penicillin 50 000 units  $\times$  4.

*Course.* For the next few days the boy became worse. Inspection of the fauces was impossible because of trismus. The abdomen became tense and there was rigidity of the neck and back. A change in colour was ascertained.

Lumbar puncture, July 4: albumin 10, globulin 0, cells 0.

Repeated pleural puncture gave no evidence of empyema.

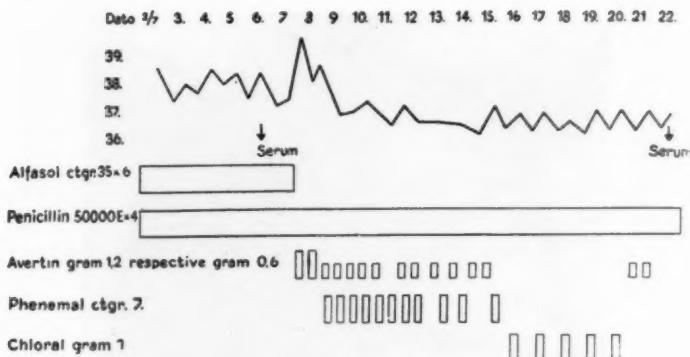


Fig. 2.

Five days after admission — *i.e.* 16 days after the first manifestation of illness — numerous attacks were observed during which the patient became stiff and cyanotic, with pronounced trismus and typical risus sardonius. He was rigid as a stick and could be raised by elevation of the head.

Now information was obtained — omitted when the history was first taken — that the boy's illness commenced with his rushing in from the garden with earth in his mouth, cough and an attack of suffocation. Thereafter there could be no doubt about the diagnosis of tetanus, and this disease as well as the pulmonary atelectasis had to be interpreted as due to aspiration of garden soil.

On Aug. 8 the boy was given 20 000 I.U. of antitetanic serum intramuscularly, and a few hours later 1 ml of tetanus anatoxin subcutaneously. He was put in a dark room by himself and given sedative treatment in the usual way with avertin, phenemal and chloral hydrate — as shown in Fig. 2. In this way further severe attacks were avoided and it was possible to give him some liquid food. Attempted inspection of the oral cavity showed that trismus was still present.

The atelectasis persisted in spite of elevation of the foot of the bed. Roentgenography on July 14 continued to show complete atelectasis of the left lung (Fig. 3).

On July 20 (13 days after injection of antitetanic serum) the condition of the patient became aggravated; besides the coughing attack, there were also attacks of tonic convulsions, cyanosis and trismus. On July 21 roentgenography showed that the atelectasis had subsided spontaneously (Fig. 4), so that bronchoscopy, which was planned, was no longer necessary.



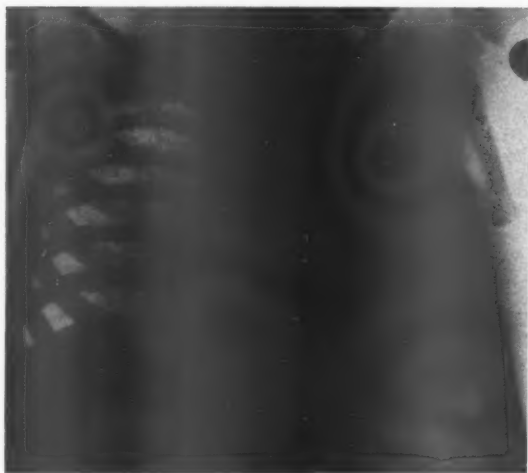


Fig. 3.

On July 22, the patient was given an injection of 5 000 I.U. of anti-tetanic serum, after which he suffered no further attacks. He improved steadily and on Aug. 11 he was discharged feeling perfectly well.

*Epicrisis.* Complete atelectasis of the left lung together with incipient trismus was demonstrated in a boy 17 months old whose illness set in with cough, attacks of suffocation and fever after aspiration of garden soil, 10 days before hospitalization.

Sixteen days after the first manifestation of illness, tetanus was ascertained, with risus sardonicus, muscular rigidity, attacks of tonic convulsions and cyanosis.

Following treatment with penicillin, antitetanic serum, tetanus anatoxin, avertin, phenemal and chloral hydrate the patient recovered from his tetanus. The atelectasis was still present 18 days after admission but subsided spontaneously following an aggravation of the tetanus.

### Discussion

In this case there was no bacteriologic or serologic evidence of infection with *Clostridium tetani*, but we consider the clinical picture to be so typical that in connection with the data of the history, the demonstrated atelectasis and the rapid effect of the serum treatment on

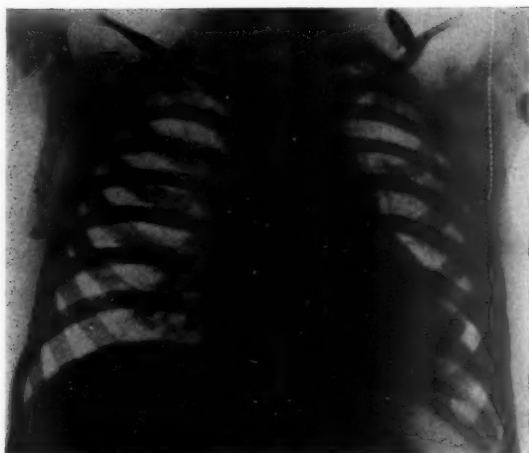


Fig. 4.

July 22 after the effect of the first serum injection may be presumed to have subsided, it makes the diagnosis as definite as possible without bacteriologic proof.

We have been unable to find any cases similar to this one, with a combination of tetanus and pulmonary atelectasis, reported in the literature, but Träina and Cilotti have reported a case of tetanus in a boy 13 years old who aspirated the tongue of a toy trumpet 12 days before admission. At first the clinical picture was characterized by cough, purulent expectoration and violent attacks of suffocation which led to the patient's hospitalization. After the foreign body had been demonstrated roentgenographically, attempts were made at superior bronchoscopy, but this was unsuccessful because the patient could not open his mouth wide enough. On the following day there were again violent attacks of suffocation and risus sardonicus was observed together with trismus, rigidity of the neck and rigidity of the abdominal and lumbar musculature. Through inferior bronchoscopy the foreign body was removed and some pus aspirated. After treatment with 270 000 I.U. of antitetanic serum, besides sedatives, the patient recovered from his tetanus after a transitory aggravation.

In this country BORRIES described in 1928 the clinical picture of ear tetanus, 9 cases of which condition had been described at that time. In some cases the disease appeared without any definite demonstrable

injury in secondary infection of a suppurating middle ear or in the cavity from a radical operation.

FRIDERICHSEN has reported a case of tetanus without any external injury in a child of 4 years who was suffering from otitis media, and he ventilates the possibility that the disease may have been otogenic in this case.

Since the publication of BORRIES' paper a dozen cases of otogenic tetanus have been described — *e.g.*, by PETZA, AGUIRRE and GOMIR, WEIL-HALLE and BORISKLOTZ, STONHAM, CORCORAN, STOUT (2 cases) and VAN DER HOEDER and JORDAN (2 cases). In the case reported by AGUIRRE and GOMIR the lesion was due to a grain of maize introduced in the external meatus, but in most of the other cases the lesion was preceded by suppurative otitis. In view of these observations it will be reasonable in cases of tetanus of unknown origin to pay attention to the possibility of an infection of the middle ear, even when such a lesion has not been recognized before.

Tetanus resulting from the presence of a foreign body in the nose has been described by SHORE, BROWN and MACDONALD, MONTES and PATERSON. In the case reported by PATERSON the origin of the lesion was disclosed when an attempt at nasal intubation revealed that one naris was blocked by three pea-sized pieces of coal. In the case reported by SHORE the foreign body was a linen-covered shirt button, in the case of MONTES a soiled piece of paper, and in the case of BROWN and MACDONALD a pearl.

Thus as a matter of fact several of the cases of tetanus in infants in whom no external injury could be demonstrated were produced by foreign bodies in the ear, nose or respiratory passages, and hence it seems not unreasonable to assume that a further percentage of these cases may have been due to foreign bodies so small that they were not noticed.

Thus MØLLER has reported 2 cases of cryptogenetic tetanus in a boy of 4 years and a girl of 5 years appearing respectively 2–3 days and 8–9 days after violent dust storms. He ventilates the possibility that the infection may have been due to inhalation of tetanus spores.

*The fact that relatively many cases of tetanus in childhood, like the one here reported, may appear without any noticeable external injury ought to be taken as an argument in favor of active immunization against tetanus.*

## Summary

A report is given of a case of tetanus and complete atelectasis of one lung due to aspiration of garden soil in a boy 17 months old. The atelectasis subsided spontaneously after having persisted for at least 18 days. The tetanus was cured.

It is emphasized that a number of cases of tetanus in childhood make

their appearance without any noticeable external injury, and that this fact ought to be looked upon as an additional argument in favor of general employment of vaccination against this disease.

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Vol. XXXIX. Fasc. 3

1950

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1950

# ACTA PÆDIATRICA

EDITOR PROFESSOR A. LICHTENSTEIN

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# ACTA PÆDIATRICA









PROFESSOR  
CORNELIA DE LANGE  
IN MEMORIAM

On January 29 Professor Cornelia de Lange died at the age of 79, after a long life entirely devoted to pediatrics. The history of her life and work is that of a medical woman, who took her profession and scientific work as a vocation, with deeply felt gratitude and awe for the inherent privilege to come into more intimate contact with the wisdom of Nature.

After her graduation in 1897 she entered general practice for a few years. After a stage in pediatrics at the university of Zürich she joined the staff of the Emma Childrens Hospital in Amsterdam in 1907. In this institution she brought pediatrics to life in her own particular way, laying full stress on accurate clinical

diagnosis and cautiously indicated therapy, as she was deeply convinced that especially in children *Vis medicatrix Naturae* is more powerful than whatever human method of treatment and should not be interfered with. In the pediatric work of that 20 years period she found many problems for scientific work, and a long list of publications bears testimony of its fruitfulness.

In 1927 she was called to the medical faculty of the university of Amsterdam as a professor and she taught pediatrics for eleven years. Her lectures were fascinating, with a fine sense of humor; they were entirely devoted to clinical pediatrics, teaching generations of coming medical men and women the importance of careful bedside observation of the sick child. Traces of this teaching can be found in the work of many pediatricians and general practitioners, who highly estimate the value of these principles to counterbalance the upswing of technical methods in medical diagnosis of these decades.

After retiring from her academical post she returned to the Emma Childrens Hospital, resuming her clinical activities now associated with important research in pediatric neuroanatomy and -pathology in the Dutch Institute for Brain Research, a special interest of hers dating as far back as 1917. In 1945 she retired from clinical pediatrics and dedicated herself entirely to this scientific work for the rest of her life; her last important paper was finished within a week before she died.

For us, her pupils, her work and personality have been inspiring until the very end of her life and her death is a very hard loss; all we can do is to continue work in the way she expected us to do.

*Ada Middelhoven.*

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## On Serious Birth Injuries of the Brain after Normal Delivery à Terme

by

CORNELIA DE LANGE †

(Part II)

The following two observations belong to the subject of the intracranial birth injury in spontaneous delivery à terme, a subject which I have treated in the volume XXXVIII of the *Acta Paediatrica*, edited in honour of Prof. A. LICHTENSTEIN. As that article had already exceeded the space allotted to each contribution, these latter observations had to be kept back and are now given separately.

I am indebted to Dr. A. DEKKER-JONKER, children's doctor in Haarlem for the excellent case history of

*Case IV.* The patient, a girl, is the second child of healthy parents, the first child is also in good health. The delivery was spontaneous at full term on 29.3. 1946 but in a very rapid tempo with vigorous expulsive pains, causing a rupture of the perineum in the mother. The first days of life were uneventful. The child was in perfect health when, at the age of 7 1/2 months, there occurred an attack of rigidity with rotation of the eyes to right and left, the right hand forming a fist and making a movement in the direction of the head. In the course of the following days these fits occurred repeatedly. The child became red in the face and rigid, the eyes were turning to the right, sometimes to the left, she stretches the left arm and bends the right one toward the head with increased tonus, both with closed fists and thumbs inward. The legs are extended with spreading of the toes. A fit lasts about one minute, sometimes at the end there are some shocks. On both feet an erythema with red pustulae appears. The fits returned and occurred, at least in the beginning of the illness, first on the right side. The child became a little down. Temperature 37.2°. An otiter and a neurologist were called in consultation. Paracentesis was performed there being a slight inflam-

mation of the drums. From the right ear there was some discharge but not otorrhoea. The following two days the condition remained unaltered, then the fits were absent for a week, but on the 15th of November they recurred. Again paracentesis was performed. There was a slight discharge from the right ear. The fits were of great frequency. On the 21st of November the child is admitted to hospital. A lumbar puncture yields a clear liquor with negative reactions of NONNE and PANDY, number of cells 5/3, total albumen 18 mg %. In a smear stained after GRAM no bacilli are found and the culture also proves sterile. During these days the temperature fluctuates between 37.5° and 38.5°. On both sides the mastoid is opened; nothing abnormal is found. A tentative diagnosis of encephalitis is made. Penicillin is given, 8 × daily 10 000 units. The operation-wounds are closing rapidly. The fits again appear, now also with clonic spasms in the face, beginning at the right corner of the mouth, there is no rigidity of the neck. The fit begins with a shock.

On the 4th of December the child is somewhat somnolent, the temperature reaches 38.5°; vomiting is noted.

Blood examination: hemoglobin Sahli 92 %, white corpuscles 12 600, rodforms 5, segments 52, eos. 2, lymphocytes 35, monocytes 6 %. Sedimentation rate 1 hour 3, 2 hours 6 mM. The feet still present a symmetrical efflorescence. Between 25 November and 4 December the temperature falls per lysin notwithstanding the penicillin therapy has been continued.

6 Dec. the fits increase in frequency. Again a neurologist is called in for consultation, in his presence some fits occur and he considers them as typically epileptic. On both sides there was twitching of the extremities. Fundus oculi normal. The tentative diagnosis of encephalitis is supported by the neurologist. His advice is to continue with penicillin, hydras chlorali during the fits and to increase the dosis of luminal to 60 mg daily.

On the 10th of December there are symptoms of a toxicosis, the next day a bloodtransfusion and an intravenous infusion of RINGER's solution are given. The child is given albumen-milk and the penicillin therapy is stopped. The temperature falls to normal. In this period there are no fits, but a real lethargy is seen, the child being only awake when being fed.

31st December the little patient is discharged from hospital, at home the lethargy gradually disappears and fits do not occur again before the 28th of January, then the child cries frequently, diarrhea and abdominal pains are noted and the fits return. The temperature is fairly normal, there is no discharge from the ears. Between the attacks the consciousness proves unimpaired. In the last days of January there is again a serious nutritional disturbance, albumen milk is given and a neurologist is called in consultation. The latter prescribes tridione which has no

success. Then vitamin B6 is given, the fits gradually decrease in frequency, but after a lapse of time they recur. The neurologist who was last called in, had prescribed a ketogenic diet which was not without effect.

The mental development of the child progresses, though of course she is rather backward but she gives by no means the impression of debilitas mentis. Between the fits she is bright, she obtains continence of bladder and bowel, she understands different things, says "yes" and attempts an upright attitude.

Now and then the child suffers from a minor inflammation of the pharynx and the fits reappear. There is a marked impression that acute infection excites the process again. A tonsillectomy is discussed but deemed inadvisable. In this way the first half of the year 1947 is passed with ups and downs. In June 1947 the child is again admitted to hospital for encephalography. A curious picture is seen, giving the impression that on the right in the A—P photo no air had entered into the subarachnoid space whereas on the left there is marked atrophy of the cortex. As will be seen later this picture was misleading and must be interpreted as caused by a technical inaccuracy. The cerebral fluid proved normal. In the period from April 1st to June 7th no fits occurred, then came a pharyngitis and together with it the fits again. Third stay in hospital from 1 till 19 of August. As highest level of temperature 37.6° is noted. Sedimentation rate after the first hour 8, leucocytes 6 700, rodforms 2 1/2 %.

Fourth stay in hospital from 11 February till 5 March 1948. Intravenous injections of tridione are given and a fasting diet. Temperature between 36.8° and 37.2°; only once 37.5° is reached. As the fits in no way could be suppressed, in July 1948 hydantol was administered, high fever resulted and a nirvanol exanthema appeared. Finally the exanthema and the fever disappeared. Then there was again a great rise in temperature, the little patient was very seriously ill and almost always unconscious. This condition lasted for weeks, fits and high fever being always present. Exitus 21 August 1948.

The post-mortem was performed by the pathologist Dr. O. H. DIJKSTRA. There proved to be a yellow, thrombosized bloodvessel on the surface of the brain and a general thrombosis of sinus, also a thrombus in the right vena jugularis and in the heart. In both middle ears pus was found. Dr. DIJKSTRA had the greatly appreciated kindness to present the brain to the Central Institute for Brain Research for further examination.

#### *Macroscopical examination*

As already said, the encephalographic picture was not confirmed by the aspect of the brain. The convexity of both hemispheres is covered

by a gray leptomeninx in which frontally, parietally and occipitally thick winding venae are present, a number of them with a yellow tinge. At the base on the right they are lacking, on the left some of them presenting the same aspect are visible. The cerebellum is cut off in the usual way through the pedes pedunculi. It also shows some yellow vessels. The fourth ventricle and the aquaeductus Sylvii are but very slightly dilated. The medulla oblongata looks normal. The cerebellum is the normal size, the nuclei dentati present their usual aspect.

A closer scrutiny reveals on the convexity of the brain a yellowish discoloration in the region of the left lobus parietalis superior, the same is true of the almost corresponding spot on the right but here it is only faintly visible.

After several pieces of the yellow vessels have been excised for imbedding in paraffin and parts cut out of the cortex at different places for imbedding in celloidin, the brain is divided into verticofrontal slices. The ventricles prove to be slightly dilated. In the lobus parietalis superior there appears an old focus of malacia extending from the cortex into the white substance of the centrum semi-ovale Vieussenii, the latter also having a yellowish tinge. The focus spreads frontally into the sensumotoric region. Also on the right a focus is found but of less extent. Both foci have softened, the right one is partly situated medially, partly dorsally. Fig. 1 and 2 show the softened parts on the left. From both foci pieces are cut off for imbedding in celloidin and in paraffin and staining after Nissl and with hematoxylin-eosin and the vertico-frontal slices represented by fig. 1 and 2 are put into MÜLLER's solution with a view to examining them after WEIGERT-PAL in order to study the myelinisation.

#### *Microscopical examination*

*Gyrus frontalis I on the left.* To the naked eye this part presents a normal appearance, nor are any microscopical changes visible, except that the pia-arachnoidea shows an increased number of cells.

*Gyrus frontalis III on the left.* In the pia and in the cortex cerebri numerous blood-vessels are hyperemic. Here also the number of uninucleated cells in the leptomeninx is larger than normal.

*Motor region on the left.* The part is taken frontally from the focus of softening. There is a limited number of small hemorrhages in the cortex, in the pia widened blood-vessels with a slight infiltration of the adventitia are seen, also the vasa vasorum show very clearly. Increased number of uninucleated elements in the pia-arachnoidea.

*Gyrus temporalis I on the left.* The brain tissue itself shows no alterations, but the meninx presents some large vessels with thrombosis, partly with a beginning of organisation.

*Gyrus temporalis II on the right is normal*



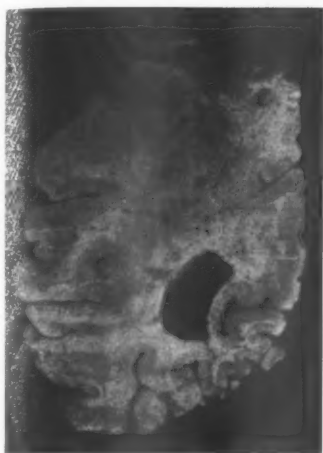


Fig. 1. Focus of malacia in the left lobus parietalis sup.



Fig. 2. The same as fig. 1 at a more caudal level.

*Uncus on the right*, brain tissue intact, no thrombosis of vessels in the meninx, but its cells have increased in number.

*Gyrus occipitalis I on the right*. At some spots there is a slight edema in the meshes of the pia-arachnoidea and an increase in cells. The vessels have widened and are markedly hyperemic.

*Focus of malacia on the left*. Here the tissue has become brittle to such a degree that on preparing the microscopical slides one finds that in some parts the cohesion is almost lost. Other parts are better preserved and even show some ganglion cells. In other spots one sees a lamina zonalis almost without a structure, the other layers have disappeared. The white substance of the cortex is totally destroyed and contains numerous "Körnchenzellen," and makrophages. Fig. 3 shows a gyrus, resembling the hollow gyrus of Fig. 2 in the article in Vol. XXXVIII but in the centre of it "Körnchenzellen" and makrophages are still present. There are recent hemorrhages but also older ones. Calcified ganglion cells, having the aspect of a spider, are clearly defined. There is a part of the cortex practically without any structure of brain tissue, but containing some blood-vessels with cuffs in the midst of some infiltrated remnants of brain tissue. The pia-arachnoidea is broad with large meshes; here and there small heaps of roundcells, a great number of makrophages and "Körnchenzellen" are present. Besides to normal vessels also some with thrombosis and partial organisation Fig. 4 (one with canalisation).



Fig. 3. Focus of malacia on the left. Exterior layer of the cortex has thickened. Beneath it a gyrus in the process of becoming hollow.

*Medial part of the right focus.* Here the leptomeninx contains only a very limited number of vessels with thrombosis, but numerous "Körnchenzellen" and makrophages. There are no inflammatory cuffs. The findings closely correspond to those on the left. Besides recent small hemorrhages the cortex shows also older ones.

*Dorsal part of the right focus.* There are no vessels with thrombosis in the meninx and no increase worth mentioning of cells. The cortex contains recent small hemorrhages as well as some older, there is marked destruction with calcified cells, locally an increase of the neuroglia. In the thin paraffin-coupees of the left focus the thrombi were examined for bacteria, but without result, nor were any found in the yellow vessels of the brain surface. Several congelation-coupees revealed in the leptomeninx and the damaged brain-tissue a large number of fat containing cells. These were locally also present in unimpaired parts of the brain but situated in the neighbourhood of damaged parts.

#### *Myelinization*

As might be expected the myelinisation in the foci of malacia was severely damaged, but the centrum semiovale had remained in a fairly good condition; the strata round the posterior horn (*Weigert-Pal's* stain) were normal.

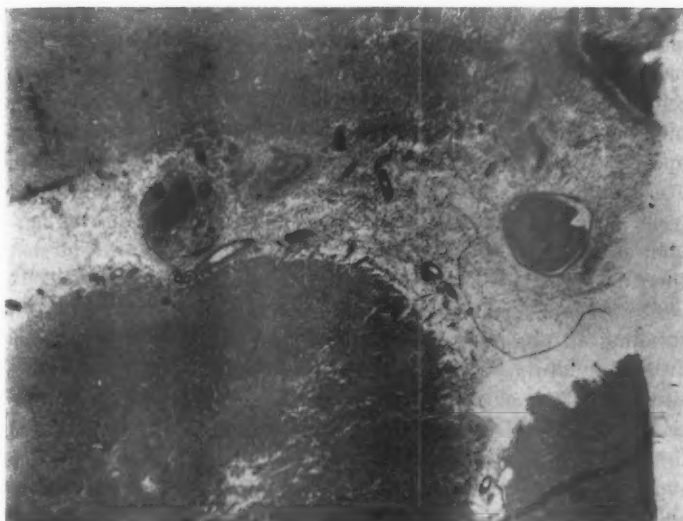


Fig. 4. Thrombosed bloodvessels in the pia above the focus of destruction.

All in all one comes to the conclusion that histologically there can hardly be any question of an inflammatory process in the brain and in the leptomeninx. It seems probable that the thrombosis of the sinus and vessels has been caused by toxins from the middle ears.

*Epikrisis.* It will meet no opposition if we attribute the convulsions or spasms which presented the character of focal epileptic fits to the foci of malacia in the cortex cerebri. At first at least, these fits always developed in the same way on the right side first while the left focus was found to be much larger than the right one. At the time when the fits presented themselves for the first, in the beginning of November 1946, the child was in excellent health, she had never yet suffered from exhausting illness during her life, nor had there been a dehydration process. The drums proved slightly inflamed and paracentesis was performed. There was some discharge from the right ear, but there was no question of an otorrhoea. Two days after the operation the fits came again in the same way, then they stopped for a week but

on the 15th of November they recurred with the same frequency and severity. Again paracentesis was performed, the right ear producing a trace of secretion. As the condition did not change for the better the child was admitted to hospital. A lumbar puncture yielded normal findings. Both processes mastoides are opened. Nothing abnormal is found. Penicillin is prescribed. The temperature fluctuates between  $37.5^{\circ}$  and  $38.5^{\circ}$  and falls per lysin. The sedimentation rate of the red corpuscles proves normal, as also the differential count of the leucocytes, except that there is perhaps a slight relative leucocytosis.

Now there remains the important question whether notwithstanding all these negative findings there has nevertheless been an inflammatory process in the os petrosum, a so-called petrositis situated in the extremity of the pyramis whence a thrombosis sinuum has developed. But indubitably such a petrositis would first have induced a thrombosis of the sinus petrosus inferior and superior, then of the cavernosus and transversus (or lateral sinus according to American designation) and not in the first place of the sinus longitudinalis superior.

Furthermore the historia morbi informs us that the little patient showed normal physical development and that there was also mental improvement. Could this have been possible with an extensive process reaching from the os petrosum via the other sinus to the sinus longitudinalis without there being a single symptom of thrombosis sinuum?

It is wellknown that a partial unilateral thrombosis of the sinus lateralis is sometimes met with as an accidental finding post mortem testifying that there had been an otitis media during life. Also we are acquainted with the fact that in infants the prognosis of a partial thrombosis is not so serious as was formerly thought. The primary thrombus without a definite etiology can occasionally heal with remnants (BYERS and HASS<sup>1</sup>, COURVILLE<sup>2</sup>). At the post mortem of our little patient pus was found in the middle ears. That this process may have led to an extensive

<sup>1</sup> R. K. BYERS and G. M. HASS, *Am. J. D. Ch.* 45 1161, 1933.

<sup>2</sup> CYRIL B. COURVILLE, *Pathology of the central nervous system*. Pacific Press publish. Ass. 1937.

thrombosis sinuum, no one will contest and one has only to bear in mind that the sinus petrosus inferior progresses to the foramen jugulare and, generally outside the cranium, combines with the vena jugularis, to understand fully that in casu a thrombus in the heart might be found. It seems possible that these thrombi are not caused by bacteria but by toxins.

From the age of  $7\frac{1}{2}$  months up to two years the child was in fairly good condition notwithstanding the recurrent fits and some intercurrent ailments. One can hardly reconcile this possibility with the presence of a general thrombosis sinuum.

Some of the thrombi found in the blood-vessels showed an organisation process, partly they were of recent date. In case III which I have described in Volume XXXVIII of *Acta Paediatrica* in a hemorrhage in the posterior horn of the right ventricle in a child which died on the 13th day of life, there was already an incipient organisation in the clot. The final illness of our little patient (case IV) which lasted for weeks certainly covers a period long enough for organisation of thrombi. The most probable explanation of the process of thrombosis sinuum is that it started in the final illness and gradually progressed. Taking this for granted, we have to look for an other explication of the foci of malacia which evidently were of earlier origin and have caused the clinical symptoms, viz. the fits beginning at the age of  $7\frac{1}{2}$  months. The most plausible interpretation in my opinion, is that they were the result of a birth injury. In favour of this opinion the fact may be taken into consideration that the delivery was a rapid one (but by no means a *partus praecipitatus*!), and that there had been vigorous expulsive pains. If, during the first days of life, symptoms of an intracranial trauma had been present, these would have been a valuable support for our diagnosis, but their absence does not at all preclude the possibility of a birth injury. It is wellknown that in many cases the cerebral symptoms only become manifest after a silent period. Probably it is necessary that the focus or the foci have attained a certain extent before they can produce clinical symptoms. In WOHLWILL's opinion which we share, in the originally damaged parts of the brain and in hitherto non-impaired

regions, the ordinary claims of daily life and all the more intercurrent illnesses, may produce destructive processes through the liability at birth acquired of the neuro-vascular system of the brain.

In general it is a sensible point of view to strive ever after an explanation of a patients symptoms as seen from the same visual angle. However, *simplex veri sigillum*, the adagium of our celebrated HERMANUS BOERHAVE, cannot cover every case and in our little patient the clinical symptoms and the anatomo-pathological findings prove most conceivable if we accept as the primary process, i.e. the cause of the foci of malacia, a birth injury and, as the secondary, a general thrombosis of the sinus spreading from a bilateral otitis media.

*Case V.* For the clinical details I am indebted to Dr. C. J. W. FRIJLINK of Amersfoort. He reports of a family with healthy parents, the girls and one of the boys being also normal, but three male children suffering from a spinal or muscular disease. The first child was seen when some months old and a diagnosis was made of WERDNIG—HOFFMANN—ORPENHEIM's disease. In the following years there was a marked improvement. The second boy resembled the first, he died at the age of five years. In the third a diagnosis of *dystrophia musculorum progressiva* (ERB) was made, the fourth is still quite normal. Dr. FRIJLINK considers the possibility of both diseases occurring in the same family.

The fifth boy was born spontaneously at full terme; he was not cyanotic, the heart action was fairly good, but the respiration insufficient and the crying very feeble. Lobelin without affect. The child died within half an hour after birth.

*Post mortem at the Anatomo-pathological Institute of the University of Amsterdam (Prof. Dr. H. T. DEELMAN)*

There proves to be a rupture at the transition of falx and tentorium, and subdural and subarachnoideal hemorrhages. Also a hemorrhage beneath the galea aponeurotica and another extra-dural one in the thoracal part of the cord. Here the spinal column shows a bloody discoloration. The section of the visceral organs show nothing abnormal, save some small hemorrhages beneath the pleura, the epicard and the capsule of the liver.

The cord in the dural sack, the cerebrum and several pieces of muscle were given me for further examination. The dural sack is removed, no hemorrhages on the cord are seen. Parts of the cord at various levels

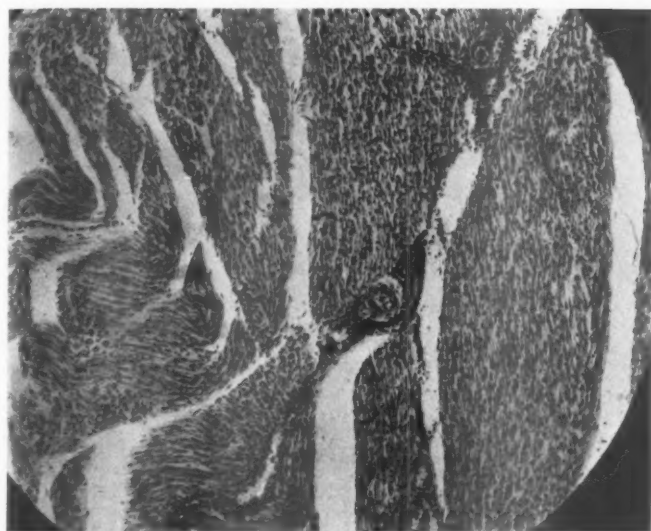


Fig. 5. Cellinfiltration in the M. Quadriceps cruris.

are examined microscopically but prove normal, the ganglion cells are in excellent condition which precludes the diagnosis of WERDNIG—HOFFMANN—OPPENHEIM's disease. The convexity of the brain and the base show nothing abnormal. The brain is cut into vertico-frontal slices, neither hemorrhages nor congenital anomalies are seen; the same is true of the brainstem and the cerebellum.

The muscles show small interstitial infiltrations of round cells surrounding the blood-vessels, the cells resemble lymphocytes; some plasma-cells are present, no polynuclears. The nuclei of the sarcolemma have not increased in number, nor is there any augmentation of the fatty tissue. The nerves look normal. The muscle fibres are somewhat thin, but the histological picture is not that of ERB's disease. (Fig. 5 a, 6.)

In my opinion it may be taken for granted that also the other male children had suffered, or are suffering from a familiar muscle dystrophy, that in this family only one single disease is found.

After this digression to the muscle-dystrophy we must return to the birth injury in the normal delivery à terme. From the anatomo-pathological description it follows that the trauma was a serious one and constituted the cause of death in this child.



Fig. 6. The same as fig. 5 with a larger magnification.

Had not the boy died within half an hour after birth, the pressure from the subdural and subarachnoideal hemorrhages on the cortex would very soon have produced irreparable damage and a yellowish discoloration would have been seen on the postmortem. If the child had survived the birth injury clinical symptoms would have followed after a certain time.

#### Summary

Two further cases are reported confirming the author's opinion that a normal delivery at full term not precludes serious intracranial birthinjuries. (Cfr AP vol. XXXVIII 1949, page 383.)

#### Résumé

On rapporte encore deux cas qui confirment l'opinion des auteurs que l'accouchement normal à terme n'exclut pas les graves lésions intracrâniennes à la naissance. (Cf. AP vol. XXXVIII 1949, page 383.)



**Zusammenfassung**

Zwei weitere Fälle werden berichtet, die die Auffassung des Verfassers bestätigen, dass eine normale rechtzeitige Geburt ernsthafte intrakraniale Geburtsfehler nicht ausschliesst. (Vgl. AP vol. XXXVIII 1949, Seite 383.)

**Resumen**

Se da cuenta de dos casos más que confirman la opinión de los autores de que el parto a término normal no excluye las lesiones graves intracranianas en el nacimiento. (Comp. AP vol XXXVIII 1949, pág. 383.)

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(FROM THE CLINIC FOR ASTHMATIC CHILDREN OF THE UNIVERSITY HOSPITAL OF COPENHAGEN (RIGSHOSPITAL) AND THE CLINIC FOR ASTHMATIC CHILDREN OF THE MUNICIPALITY OF COPENHAGEN AT THE QUEEN LOUISE CHILDREN'S HOSPITAL)

## **On Universal Reactions in Connection with Treatment of Asthmatic Children with Bacterial Vaccines**

By

**E. WINGE FLENSBORG**

Universal reactions in connection with vaccine treatment of presumably bacterial-allergic asthmatic children have been described by a number of authors.

COOKE (1) thus gives a summary description of such reactions, mentioning that attacks of asthma may occur even after quite small doses of vaccine, as a rule only from 12 to 48 hours after injection. He recommends circumspection and stresses the occurrence of cases in which repeated injections of vaccine administered without any regard to possible reactions have kept the patient in status asthmaticus. Further, he considers that these asthmatic reactions to even quite small doses of vaccine are perhaps the most convincing criteria of the allergic nature of "infective asthma".

CRUMP (2) reported vaccine reactions (attacks of asthma) in 11 out of 112 asthmatic children treated with autogenous vaccine. In 2 of these cases attacks of asthma occurred several times in connection with injections of vaccine, in one child on every increase of the dose.

In children suffering from uncomplicated infective asthma STEVENS (8) observed four different forms of reaction to treatment with filtrates of cultures of pathogenic bacteria from the upper respiratory tract: (1) chills and fever for one or two days (in 5 %), (2) excessive swelling at the site of injection, (3) transient attacks of asthma, occurring from six to twelve hours after the

Ages (Years)	Number Children Treated With Vaccine	Number Children Reacting to			Total Number Children Reacting	%
		1st Dose	Subsequent Dose (No Reaction to 1st)	Both 1st and Subsequent Doses		
0—1	2	1	0	1	1	45
1—2	15	3	2	3	5	
2—3	12	4	3	2	7	
3—4	15	5	2	2	7	33
4—5	16	4	1	1	5	
5—6	18	1	3	1	4	
6—7	13	2	2	1	4	17
7—8	3	0	0	0	0	
8—9	14	0	1	0	1	
9—10	21	3	2	3	5	21
10—11	11	1	0	0	1	
11—12	2	0	1	0	1	
12—13	9	0	0	0	0	5
13—14	8	0	1	0	1	
14—16	3	0	0	0	0	
Total	162	24	18	15	42	26

Fig. 1. Incidence of vaccine reactions at different ages.

injection (observed in 64 % of the treated children at some time during treatment), and (4) an almost continuous asthmatic state in case of repeated overdosage (5 %).

Recently O'CONNOR (9) reported on cases of asthma produced by treatment with filtrates of bacteria introduced into the organism by nasal instillation.

A preceding communication (FLENSBORG, NEERBORG and SAMSØE-JENSEN (5)) gives an account of the technique and the dosage used so far in the treatment with a standard vaccine ("vaccine for the treatment of asthma") of asthmatic children suffering from presumably bacterial allergy.

Since in spite of very cautious dosage and, in most cases, great care with a view to possible slight reactions to injections

of vaccine, we have nevertheless observed quite a great number of more and less severe reactions, we should like to impart our experiences to others.

The *series of cases* comprises 162 well observed asthmatic children who were either admitted to hospital during treatment or were treated as outpatients at a clinic for asthmatic children. In the latter cases the mothers were enjoined to observe any reactions closely, including rises of temperature.

One or more vaccine reactions occurred in a total of 26 % of the treated children. The incidence of vaccine reactions in relation to the ages of the children is shown in Fig. 1. It appears that a far greater number of reactions occur in children under 6 years of age than in older children, and particularly during the first 3 years of life a reaction to vaccine is common.

#### (1) Reactions to the First Injection of Vaccine

An analysis hereof in relation to age and the initial dose administered (Fig. 2) shows that it would be justifiable to attempt to reduce the initial dose in the first 4 years of life to 5 000 bacteria (0.1 cc of 0.05 million bacteria per cc), since no less than 6 out of 16 children in this age group displayed reactions to a first dose of 50 000 bacteria.

Similarly, an initial dose of 50 000 bacteria in the age group 4 to 7 years should undoubtedly be preferred to the initial dose of 0.5 million bacteria now used.

*The nature of the reactions* after the first injection of vaccine was — unlike the frequency — independent of age.

A classification of the reactions according to their nature and severity shows the following conditions:

*Severe reactions* (6 patients).

Attacks of asthma: 3 patients, including 2 with simultaneous high temperatures (4, 2 and < 1 year).

High temperature and asthmatic wheezing: 1 patient (6 years).

High temperature: 2 patients (4 and 9 years).

Ages (Years)	Number Children	Number Children Reacting to 1st Dose	Number Bacteria in 1st Dose (+ Reaction, - No Reaction)											
			500		5,000		50,000		0.5 mill.		5 mill.		10 mill.	
			+	-	+	-	+	-	+	-	+	-	+	-
0—1	2	1					1	1						
1—2	15	3	0	1	0	2	1	5	1	2	1	0	0	1
2—3	12	4					2	4	2	4				
3—4	15	5			0	1	2	0	3	8	0	1		
4—5	16	4							3	12	1	0		
5—6	18	1							1	16	0	1		
6—7	13	2							2	7	0	4		
7—8	3	0							0	3				
8—9	14	0							0	11	0	3		
9—10	21	3					0	1	2	7	1	9	0	1
10—11	11	1					0	1	0	3	1	6		
11—12	2	0					0	1	0	1				
12—13	9	0							0	8	0	1		
13—14	8	0							0	5	0	2	0	1
14—16	3	0							0	3				
Total	162	25 (15 %)												

Fig. 2. Relation between reaction to first dose of vaccine and age and dose.

*Medium severe reactions* (8 patients).

Asthmatic wheezing: 1 patient (10 years).

Asthmatic wheezing and catarrhal affection: 4 patients (1, 2, 3 and 9 years).

Asthmatic wheezing and subfebrile temperature: 2 patients (2 and 4 years).

Asthmatic wheezing, catarrhal affection and subfebrile temperature: 1 patient (1 year).

*Slight reactions* (10 patients).

Subfebrile temperature: 6 patients (3, 4, 4, 5, 6 and 9 years).

Catarrhal affection: 4 patients (1, 3, 3 and 3 years).

The time of onset of the reaction (after the first injection) averaged 48 hours, varying from one to four days. However, a

single severe reaction occurred as early as six hours after the first injection of vaccine. The time of onset seems to be independent of the age of the child.

In the cases where part of the reaction, or the only reaction, was a rise of temperature, the average duration of the latter was 18 hours, varying from 12 hours to three days. In one case, however, a subfebrile temperature persisted for two weeks without any other demonstrable cause than the first injection of vaccine. The highest temperature measured was 39.6° C.

The duration of the entire reaction following the first injection of vaccine also seems to be independent of the age of the child, and averaged a little more than four days, varying from one day to several weeks, but most frequently lasting from 1 to 3 days.

## (2) Reactions to Subsequent Injections of Vaccine

Of such reactions 63 were observed in 33 patients (20 %). They were ascertained with highly varying doses and at very different times in the course of the vaccine treatment.

*Severe reactions* (26 reactions in 18 patients).

Attacks of asthma: six times in 5 patients (3, 4, 6, 7 and 11 years).

Attacks of asthma and high temperature: five times in 3 patients (2, 3 and 4 years).

Attacks of asthma, subfebrile temperature and catarrhal affection: four times in 4 patients (1, 2, 3 and 6 years).

High temperature: seven times in 7 patients (1, 1, 2, 2, 5, 9 and 13 years).

High temperature and asthmatic wheezing: twice in 1 patient (3 years).

High temperature, asthmatic wheezing and catarrhal affection: twice in 2 patients (2 and 6 years).

*Medium severe reactions* (24 reactions in 17 patients).

Asthmatic wheezing: 14 times in 7 patients (2, 3, 3, 7, 9, 9 and 11 years).

Asthmatic wheezing and catarrhal affection: twice in 2 patients (1 and 3 years).

Asthmatic wheezing and subfebrile temperature: three times in 3 patients (3, 4 and 9 years).

Asthmatic wheezing, subfebrile temperature and catarrhal affection: five times in 5 patients (1, 2, 2, 6 and 8 years).

*Slight reactions* (13 reactions in 12 patients).

Subfebrile temperature: five times in 5 patients (1, 2, 4, 9 and 9 years).

Catarrhal affection: four times in 4 patients (1, 3, 3 and 5 years).

Subfebrile temperature and catarrhal affection: four times in 3 patients (1, 9 and 11 years).

(The total number of patients with severe, medium severe and slight reactions was higher than the 33 stated, as some of the patients had several reactions of varying severity.)

The time of onset of the reactions (after subsequent injections of vaccine) averaged 48 hours, varying from half a day to four days. Attacks of asthma on the sixth day after the injections occurred in only one patient, after 3 different injections.

The duration of the rises of temperature averaged two days, varying from one half to five. The highest temperature measured was 39.8° C.

The duration of the entire reaction to subsequent injections of vaccine averaged five days, varying from one to fourteen.

A comparison between the various findings in the case of vaccine reactions to the first and to subsequent injections of vaccine (Fig. 3) shows that there is no great difference, apart from the fact that there was a comparatively greater number of severe reactions after the subsequent injections of vaccine. In view of the fact that the frequency of subsequent vaccine reactions seems to be a little higher than that of reactions to the first injection, the increase in the dose of vaccine prescribed by the table generally employed (FLENSBORG, NEERBORG and SAMSOE-JENSEN (5)) is presumably a little too great.

Frequency (% Children Treated With Vaccine)	Reaction to 1st Injection	Reaction to Subsequent Injection
	15 %	20 %
Time of Onset of Reaction (After Injection)	2 days ( $\frac{1}{2}$ —4)	2 days ( $\frac{1}{2}$ —6)
Duration of Reaction	4 days (1 day—several weeks)	5 days ( $\frac{1}{2}$ —5)
Maximum temperature	39.6° C	39.8° C
Duration of Rise in Temperature, If Any	1 $\frac{1}{2}$ days ( $\frac{1}{2}$ —3)	2 days ( $\frac{1}{2}$ —5)
Distribution of Severity of Reactions in Relation to Total Number	Severe	6 (25 %)
	Medium Severe	8 (33 %)
	Slight	10 (42 %)
		26 (41 %)
		24 (39 %)
		13 (20 %)

Fig. 3. Comparison between reactions to first and subsequent injections of vaccine.

A few examples may be stated in order further to illustrate the vaccine reactions:

*Case 1* (F. pr./49). A patient aged 6 years suffering from asthma and vasomotor rhinitis; ill from infancy. No definitely established releasing factors. Cutaneous reactions faintly positive for purified extract of house dust, others negative. As bacterial allergy seemed a possibility, a test dose of "vaccine for the treatment of asthma", 0.5 mill. bacteria, was administered. Six hours later the patient became restless and developed headache, cough, asthmatic wheezing and vomiting with mucus, but no material dyspnoea. The temperature was not taken until 14 hours after the injection: 38.6° C, rising to 39.5° C and falling to normal in the course of two days. Seven days later wheezing and cough still persisted. Five days after the reaction had subsided, another injection was given, this time 5 000 bacteria (1/100 of the first dose). About 20 hours later the patient developed a marked hissing and wheezing accompanied by a strong, irritating cough. The symptoms persisted for 9 days. The next dose was not administered until one week after reaction No. 2 had



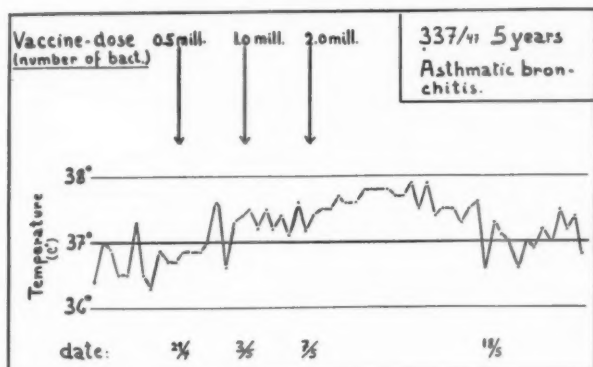


Fig. 4.

subsided. A dose of about 500 bacteria only (1/1000 of the first dose) was administered. This also produced a reaction, though it was only a slight one. As the general practitioner misunderstood the directions for treatment, rising doses were administered during the weeks that followed (500—1 000—2 000—3 500 bacteria per injection), and following each injection increasingly violent reactions now occurred, with markedly asthmatic troubles but no fever. When I saw the patient again after a month he was in status asthmaticus, and consequently the treatment was discontinued.

This must be a case of unusually marked bacterial allergy, and after a prolonged "rest pause" attempts will be made with homoeopathic doses increased very cautiously.

*Case 2 (R. H. 337/47. Fig. 4).* A 5 year old patient. Diagnosis: bronchitis asthmatica, asthma bronchiale. Cutaneous reactions negative. The disease developed after whooping cough. All the asthmatic manifestations of this patient appear after a few days of catarrhal affection. No other releasing factors are known. The temperature was normal and there were no asthmatic symptoms when treatment with "vaccine for the treatment of asthma" was instituted (April 29). Two days after the first injection (0.5 mill. bacteria) there was a slight subfebrile temperature. In spite of this the dose was increased to 1 mill. bacteria in the next injection (May 3). Following this there was constantly a slightly increased temperature in the morning. On May 7 the patient was given the third injection (2 mill. bacteria) and then had a distinctly subfebrile temperature for 10 days. No asthmatic symptoms, but now and again night cough. No other cause of the subfebrile temperature could be demonstrated.

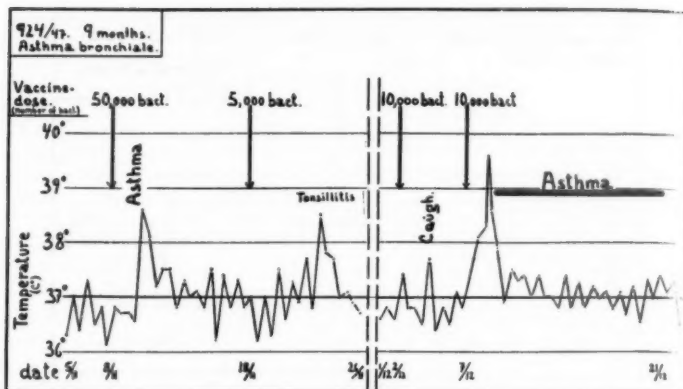


Fig. 5.

Case 3 (R. H. 924/47. Fig. 5). Nine months old. From the age of 2 months some wheezing in the chest has been observed, constantly present during the last five or six months. During the first week after admission there were frequent periods of hissing, wheezing respiration, in particular when the patient was excited, and on a single occasion there was distinct dyspnoea simultaneously. Diagnosis: presumably asthma bronchiale. X-ray of the lungs: nothing abnormal. Cutaneous reactions negative. When, on November 8, there had been no wheezing for some days the patient was given "vaccine for the treatment of asthma", 50 000 bacteria. About 30 hours afterwards the patient developed cough and increasing dyspnoea which in the course of 18 hours passed on to a regular attack of asthma. On the next day there was a rise of temperature ( $38.6^{\circ}\text{C}$ ) which persisted for well over 48 hours. This was followed by coryza and mucous râles for a few days.

After the reaction had worn away completely another injection (5 000 bacteria) was given on November 18. No unquestionable reaction to this, but from November 22 to 25 the patient had acute tonsillitis. A third injection on December 2 (10 000 bacteria) produced a slight subfebrile temperature and increased cough on the second day after the injection. As it was not quite certain whether this was actually a vaccine reaction, the same dose (10 000 bacteria) was given in the next injection on December 7 for safety's sake. As early as 48 hours after this injection the patient's temperature rose, in the course of the next 24 hours to  $39.6^{\circ}\text{C}$ , after which it fell by crisis. At the same time asthmatic wheezing and a dry cough set in, and in the course of the next 11 days numerous small attacks of asthma occurred. When this reaction had

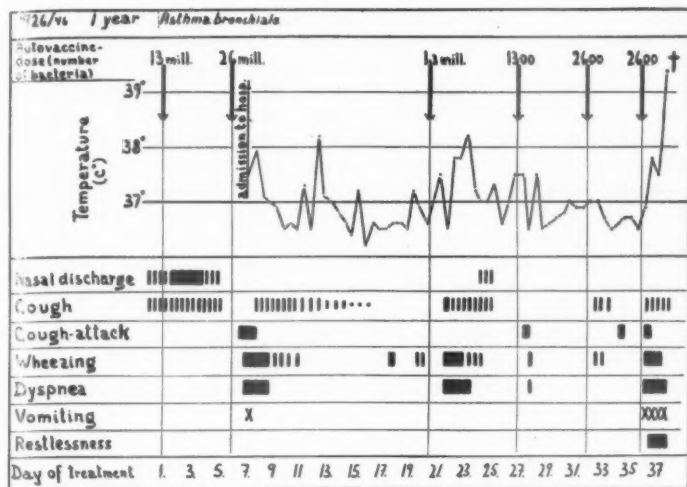


Fig. 6.

subsided completely an injection of about 500 bacteria was given (on December 29) without producing any reaction, and it was now possible to increase the dose of the next injections (500—1 000—2 500—4 000 bacteria per injection) without producing any reactions.

*Case 4* (R. H. 926/46. Fig. 6). A 1 year old patient (not included in the statement of the frequency of the vaccine reactions, etc. This was the case causing us to register the vaccine reactions more exactly during the years that followed. — Fig. 6).

The patient was largely in good health until the age of about 9 months. Began at that age to develop a dry irritating cough for periods, both day and night. At the age of 11 months anaemia was ascertained. Following coryza and sneezing at the age of 1 year, the child suddenly had a violent persistent fit of cough and great unrest, and in the course of 12 hours there developed increasing hoarseness and dyspnoea with a subfebrile temperature. Upon admission to hospital the child displayed slight dyspnoea with retractions, a harsh respiration with scattered medium râles, redness of the fauces, and slight hoarseness (tracheobronchitis et laryngitis acuta). Was treated with steam and soon improved. During the stay in hospital, swabs were taken from nose and throat for the preparation of autogenous vaccine, which was used by the general practitioner for treatment after discharge.

*First dose of autogenous vaccine: 130 mill./cc, 0.1 cc (i.e. 13 mill. bacteria).* In connection with this injection the cold aggravated a little with coryza and cough (the patient had been catarrhal since discharge from hospital). *Second injection, 5 days later, 26 mill. bacteria.* A few hours after this injection a violent cough developed as if the child had swallowed something the wrong way; this cough persisted for 24 hours and in time was accompanied by a fairly pronounced expiratory dyspnoea with much vomiting. On admission to the department the day after the second injection of vaccine the patient was exhausted and inert, with distinct expiratory dyspnoea with retractions. No special effect was obtained with tablettae novatrophedrin, but the injections of adrenalin were helpful. In the course of the day the wheezing recurred but was obviated by adrenalin.

Examinations: cutaneous reactions negative. Leukocyte figures: 15 200 with 5 % eosinophils; micro-sedimentation rate 11 mm/1 hour; x-ray of lungs: nothing abnormal; x-ray of the oesophagus and the trachea: nothing abnormal.

During the days that followed there was periodic wheezing and a harsh cough, and a fortnight after the second injection there was still some wheezing during the night. Fifteen days after the second, *another injection of vaccine was given (1.3 mill. bacteria) (III).* During the night (about 12 hours after the injection) a more pronounced wheezing and dyspnoea occurred. Adrenalin had no great effect, but some effect was produced by euphyllin suppositories and novatrophedrin. During the days that followed both harsh coughing and periodic wheezing persisted and a slight temperature reaction occurred on the second to third day after the injection. Six days after the injection the patient was free from symptoms again, and on the seventh day an injection of *autogenous vaccine (IV), 1 300 bacteria*, was given. About 12 hours later the patient had a violent fit of coughing, followed by slight wheezing and dyspnoea but no rise of temperature. Five days later *an injection of 2 600 bacteria was given (V).* Twelve and 15 hours after the injection, slight wheezing and cough which subsided spontaneously. During the night that followed there was some cough and the next night a violent fit of cough; no rise of temperature. The next injection, 4 days later, contained the same dose: *2 600 bacteria (VI).* About 10 hours later a violent fit of cough occurred, followed by a short, intermittent cough which was soon accompanied by wheezing and dyspnoea. Novatrophedrin exerted no effect. In the course of the day the patient, who was sinking rapidly, was pale, faint, whimpering and peevish, restless, and, to a varying degree, dyspnoeic. There were repeated vomitings, gradually sanguinolent. The dry hacking cough persisted. The case did not resemble an actual attack of asthma; the predominant features were the unrest, the cough, and the exhaustion. Euphyllin exerted no effect and the unrest remained uninfluenced by bromisoval and phenylethyl bar-

bituric acid (10 cg) in intramuscular injection. Auscultation of the lungs revealed a slightly prolonged expiration, an increased respiratory rate and a few medium râles, but no ronchi. The temperature was now rising and the child was sinking rapidly. Treatment with penicillin and alphasol was instituted and a subcutaneous fluid supply (bicarbonate) provided, as moderate acidosis was present. The child was placed in an oxygen tent and given adrenalin, which produced no effect. Repeated aspiration removed copious, tenacious mucus. Stimulation remained ineffective. There occurred a period of violent unrest, resembling an encephalitic state, and then the patient rapidly sank further. Death occurred a little over two days after the sixth injection of autogenous vaccine.

*Post-mortem examination* (G. Teilum). — Bacteriological examination: no growth. The general autopsy showed a rather extensive purulent bronchitis with scattered atelectatic and emphysematous areas, but otherwise nothing abnormal, apart from hyperplasia of the mesenteric lymph nodes.

*Microscopic examination.* — Lungs: dense accumulations of polymorphonuclear leukocytes, in several areas choking the bronchi completely. These were particularly abundant around the bronchi, where dense layers of leukocytes and histiocytes were seen. Further, quite extensive peribronchial fibrosis was noted; the vessels were much dilated and blood-clogged both in the peribronchial connective tissue and the alveolar septa. No eosinophilia or allergic changes were seen. The pulmonary tissue itself displayed a mixture of emphysematous areas with dilated alveoles and pneumonic areas, appearing partly in the form of dense infiltrations of histiocytes surrounded by red blood corpuscles infiltrating the alveolar septa, and partly as scattered accumulations of histiocytes as well as leukocytes in the alveoles proper. There were no signs of any specific inflammation. Liver: nothing abnormal, apart from some acute stasis corresponding to the central part of the acini. The pancreas, the spleen, and a lymph node from the mesentery displayed nothing abnormal.

*Discussion of Case 4.* — On the first admission to hospital the child's disease was considered to be tracheobronchitis and laryngitis (laryngismus stridulus), but it is quite possible that the case was actually one of asthmatic reaction (very persistent fits of cough and dyspnoea) even then; in this connection it is worth mentioning the periodic, dry, irritating cough from which the child suffered for three months prior to the first admission, a cough typical of that frequently present in small asthmatic children.

Following the first dose of vaccine there was undoubtedly a reaction, though not of the asthmatic type, but when the dose of vaccine was doubled in the next injection, a severe, rapid asthmatic reaction set in. One tenth of the original dose of vaccine administered after the second

vaccine reaction had subsided released another severe asthmatic reaction, and therefore the next dose was only 1/10 000 of the original first dose. Even this minimal dose produced a slight asthmatic reaction, which seems to indicate that the preceding injections may have sensitized the child further, since the first injection did not produce any asthmatic reaction. The next injection (2 600 bacteria) produced so slight a reaction that, with our limited knowledge of vaccine reactions at that time, we did not hesitate to administer the same dose in the sixth injection of vaccine which so surprisingly led to the fatal reaction. This was peculiar in that it was asthmatic only to a certain degree; the predominant features were alternately a violent motor unrest such as may be seen in acute encephalitis and an apathetic shock-like state. There was a slight acidosis which cannot explain the clinical picture. Acute cerebral oedema may have formed part of the reaction, but unfortunately no autopsy of the brain was made.

### Discussion

There seems to be no doubt that at any rate some of the 87 universal reactions reported here in asthmatic children treated with vaccines of pathogenic bacteria from the upper respiratory tract were of an allergic nature. The reactions may perhaps with some justification be divided into two groups: (1) those in which only catarrhal affections and/or a rise of temperature occurred, without any asthmatic symptoms, and (2) reactions of an asthmatic stamp (regular attacks of asthma, asthmatic wheezing, and fits of cough). The former reactions may not have been of an allergic nature; similar reactions may be seen after the administration of diphtheria and other bacterial vaccines to normal non-allergic children. However, it is striking that in several asthmatic children purely pyretic-catarrhal reactions were observed alternating with purely asthmatic reactions, in some cases even to the same doses of vaccine. This seems to indicate that there is no fundamental difference between the two kinds of reaction.

A comparison with the constitutional reactions which may occur in connection with intradermal tests and injection treatment with "genuine" allergen extracts shows a number of points of resemblance with, but also several decisive differences from, the reactions which may result from the treatment with vaccine (see Fig. 7).

	Universal Reactions After Injection of	
	"Genuine" Allergen Extracts	Bacterial Vaccines
Frequency	1 to 10 % (in adults)	10 to 65 % (in children)
Time of Onset of Reaction After Injection	(1) most frequently: <i>at once</i> , or within an hour; (2) rarely: in the course of several hours or days (?).	<i>Late</i> (averaging 48 hours after the injection — varying from $\frac{1}{4}$ to 4 days).
Symptoms of Reactions	<i>Slight reactions:</i> discomfort, languor, universal sensation of pain, moderate rise of temperature (as a rule only for a few hours).  <i>Severe reactions:</i> severe itching of the skin, urticaria, angio-neurotic oedema, symptoms of Hay fever (coryza, sneezing, tickling of the nose, epiphora, conjunctival irritation), asthmatic symptoms (dry, irritating cough, wheezing, attacks of asthma of varying severity). Diffuse erythema of varying severity with sensation of heat. Circulatory collapse. Acute abdomen. Rarely: headache, dizziness, tachycardia.	<i>Slight reactions:</i> subfebrile temperature, possibly with coryza; cough and râles.  <i>Medium severe reactions:</i> asthmatic wheezing, with or without simultaneous, moderate rise of temperature, and catarrhal affection.  <i>Severe reactions:</i> attacks of asthma and/or high temperature, possibly associated with catarrhal symptoms.  Only observed once or in few cases: unrest, headache, vague pain in the extremities, marked congestion of face with conjunctival irritation.
	In case of continued treatment without regard to the condition, status asthmaticus may occur.	Dito.
	Deaths have been reported.	No deaths reported previously.

Fig. 7. Comparison between universal reactions produced by "genuine" allergen extracts and bacterial vaccines.

*The frequency of reactions* to treatment with bacterial vaccine is presumably far greater than to treatment with "genuine" allergen extracts. Universal reactions to bacterial vaccine have been observed by us in 26 % of the children treated, and on the basis of treatment of about 2 000 asthmatic children, it is my personal experience that these reactions are far more frequent than reactions to treatment with "genuine" allergen extracts, even if I cannot support this impression by statistics.

This view is, however, also supported by a few communications in the literature on the subject wherein the frequency of universal reactions to bacterial vaccine in children is given as 10 % (CRUMP (2)) and 65 % (STEVENS (8)), whereas frequencies varying from 1 to 10 % (see SCHWARTZ (6)) are given for universal reactions to "genuine" allergen extracts.

As to the cause of these different frequencies, we can only surmise. There may be significance in the fact that the treatment with bacterial vaccine is instituted without any other guidance whatever than the patient's clinical condition, whereas the treatment with "genuine" allergen extracts is started on the basis of the intensity of the reactions of the skin, so that the treatment is instituted precisely with the lowest concentration of the extract to which the patient just shows a positive reaction in intradermal tests. This may possibly be a contributory cause of the large number of vaccine reactions following the first injection.

Furthermore, it is not inconceivable that the different age distribution may play a part in the different frequency of reaction to "genuine" allergen extracts and to injections of bacterial vaccine, since the latter form of treatment is used chiefly for children in the first years of life, whereas allergen extracts are generally administered to children in the older age groups. And this assumption is supported by the present series of cases, which just show a far higher percentage of reactions in the lower age groups than in the higher ones.

*Will it be possible in any way to counteract the frequent occurrence of vaccine reactions?*

As already mentioned, on the basis of the results of the present examination (Fig. 2) we recommend reduction of the initial dose



in the younger age groups. This will presumably lead to fewer reactions caused by first injections.

The occurrence of reactions later in the course of treatment may perhaps be counteracted by a more cautious rise than has been used so far (FLENSBORG, NEERBORG, SAMSOE-JENSEN (5)).

The following dosage is suggested:

*Initial dose:*

9 months to 4 years: 5 000 bacteria (0.1 cc of 0.05 mill./cc);

4 to 7 years: 50 000 bacteria (0.1 cc of 0.5 mill./cc);

over 7 years: 500 000 bacteria (0.1 cc of 5 mill./cc).

In case universal reactions, whether slight or severe, occur after these initial doses, the next dose should not be administered until the reaction has been completely obviated, and it should then be reduced to one-tenth.

The following more cautious dosage may also be tried (within each concentration of the vaccine): 0.10—0.15—0.20—0.30—0.45—0.65—0.90 cc, after which the next concentration, ten times higher, is administered.

Careful recording of the patient's condition, including his temperature, especially during the first four days after each injection of vaccine, is required, as it will thus be possible to discover slight reactions. We have observed several times that when such a slight reaction has been ignored, the next injection, with an increased or even with the same dose, has produced a severe reaction.

However, even the greatest care and circumspection in fixing the dose cannot prevent the occurrence of universal reactions, as the sensitiveness of the patients to the bacterial vaccine may apparently vary in a capricious way. This is illustrated by the following example.

*Case 5.* (K. K. Clinic for Asthmatic Children, 17/49.) — A 3 year old patient tolerated the following doses in 3 consecutive injections: 50 000—100 000 and 200 000 bacteria. Then followed an interval of one month. To be on the safe side the next dose was then reduced to 5 000 bacteria (1/40 of the one last administered) and no reaction occurred. A week later a dose of 10 000 bacteria was administered. The next day there occurred asthmatic wheezing and a rise of temperature

(38.7° C at the utmost) which to begin with was not considered a vaccine reaction, and consequently the next injection, after the course of a week, consisted of 12 500 bacteria. The next day the patient displayed precisely the same symptoms as after the preceding injection. The next injection of 5 000 bacteria produced no symptoms, and the patient then tolerated a cautious increase in the dose.

There can hardly be any doubt that this case displayed vaccine reactions to doses which were, respectively,  $\frac{1}{12}$  and  $\frac{1}{4}$  of the dose tolerated a month before.

The greatest distinction between the reactions to bacterial vaccine and the reactions to "genuine" allergen extracts is *their time of onset*. The vaccine reactions are *late* manifestations, whereas those observed after the injection of allergen extracts most frequently appear *at once*, or at least within the first hour following the injections. In some cases they appear later. COOKE (1) thus considers that 33 % of the constitutional reactions after injection of "genuine" allergen extracts appear later than one hour after the injection, and believes that he has observed so late a reaction as five days after the injection. SCHWARTZ (6) reported a case in which a constitutional reaction occurred four hours after cutaneous testing with "Helisin" (pollen extract). The earliest vaccine reaction observed by us occurred six hours after the injection of vaccine; further, we have observed one 12 hours and one 18 hours after the injection, while all the other reactions appeared only over 24 hours after the injection.

This difference in time shows that there must be a fundamental difference between the mechanisms underlying the reactions, even if we consider both as being of an allergic nature. It may perhaps be that it is not the bacteria themselves but either their decomposition products or perhaps substances produced by the defensive measures of the organism against the bacteria that act as allergens.

A comparison between *the symptoms of the two kinds of reaction* shows that symptoms of the skin and of hay fever are quite common reactions to injections of "genuine" allergen extracts, whereas these symptoms are never seen after injections of vaccine. Nor has circulatory collapse been observed in the latter case. On the

other hand, asthmatic symptoms and a rise of temperature may occur after both kinds of injection. In the patient who had the shortest lag period observed the symptoms bore a great resemblance to the slight reactions described by DERBES and ENGELHARDT (3) after injections of "genuine" allergen extracts (unrest, headache, vague pain in the extremities) but this patient had fever and asthmatic respiration as well.

Continued treatment without proper regard to reactions, both with allergen extracts and with vaccine, may produce status asthmaticus (cf. SECHER (7) and Case 1 of the present series).

As far as I know, there have been no previous reports of deaths caused by treatment of asthmatic children with bacterial vaccine. But there are several communications of deaths as a consequence of severe constitutional reaction following the injection of "genuine" allergen extract, either in severe circulatory collapse or as a consequence of status asthmaticus.

In Case 4 of the present series it is most probable that the patient's death was due to an unexpectedly strong reaction to the same small dose of vaccine that, when administered four days earlier, released only a weak reaction.

#### **Treatment of Patients Displaying Reaction to Vaccine**

The best form of treatment is prophylactic: administration of a small initial dose which should be cautiously increased with close supervision of even slight reactions.

If a reaction to the vaccine occurs, no treatment is required in mild cases. In medium severe cases with asthmatic wheezing, *tablettae novatrophedrini* ("DAK") or *tablettae idophedrini*,  $\frac{1}{2}$  to 1 tablet, should be administered immediately and repeated as required up to five times in 24 hours. If this does not obviate the reaction, one should not hesitate too long to give an injection from 0.15 to 0.30 cc of adrenalin, the dose depending on the age of the child and the severity of the reaction.

In severe reactions with regular attacks of asthma, *novatrophedrin* or *idophedrin* may also be tried first, but if no effect is produced in the course of 15 to 20 minutes, an injection of

adrenalin should be given, and this should be repeated until the reaction is under control. Children tolerate injections of adrenalin very well and they may be repeated several times in 24 hours. Simultaneous institution of a continuous dosage of novatrophedrin and large doses of iodine (e.g. kalii jodidi gm 15—200, 10 gm three or four times daily) is recommended.

As a rule, the rise of temperature requires no special treatment; it is transient in most cases and hyperpyrexia has never been observed by us.

As previously pointed out by COOKE (1), the occurrence of so frequent and, in many cases, severe asthmatic reactions to injections of even minimal doses of vaccine supports the assumption of the presence in such asthmatic children of an allergy to the pathogenic bacteria of common occurrence in the upper respiratory tract, or rather to the decomposition products of the bacteria, or to substances produced by the defence of the organism against the bacteria. The fact that this allergy cannot be demonstrated directly by clinical methods, for instance by means of cutaneous tests with bacteria or filtrates of bacteria as in the "genuine" allergies, does not by any means invalidate this theory.

### Summary

1. In 162 asthmatic children treated with vaccine of ordinary pathogenic bacteria from the upper respiratory tract, 63 universal reactions were observed in 42 patients (26 %); 24 (15 %) reacted to the first dose, while 33 (20 %) had one or more reactions later in the course of the treatment. Highest frequency of reactions during the first four years of life.

2. The reactions may be classified as *slight* (catarrhal affection and/or subfebrile temperature), *medium severe* (asthmatic wheezing with or without subfebrile temperature and catarrhal affection), and *severe* (attacks of asthma and/or high temperature). Severe forms were more frequent in later reactions than in the first one.

3. The time of onset of the reactions averaged 48 hours after the injection.

4. Repeated overdosage without regard even to slight reactions may produce status asthmaticus or a persistent rise of temperature.

5. A fatal case is reported in which death was presumably caused by an injection of vaccine containing only 2 600 bacteria in a 1 year old patient who previously displayed only a very slight reaction to the same dose. This case and others (which were not fatal) illustrate that the sensitiveness of the patients to the bacterial vaccine may vary widely and indicate the importance of close supervision and very cautious dosage of bacterial vaccines for patients suffering from asthma.

6. The reactions after "genuine" allergen extracts may vary far more than after bacterial vaccines. The former are furthermore frequently immediate reactions, the latter late ones.

7. The universal reactions of asthmatic nature, which frequently follow even small doses of bacterial vaccine support the assumption of the presence in such children of an allergy to bacteria, to the decomposition products of the bacteria, or to substances produced by the organism's defensive measures against the bacteria.

### Résumé

1. Chez 162 enfants asthmatiques traités au vaccin de bactéries pathogéniques ordinaires de la région respiratoire supérieure, 63 réactions universelles ont été observées chez 42 sujets (26 %); 24 (15 %) ont réagi à la première dose, tandis que 33 (20 %) ont eu une ou plusieurs réactions plus tard au cours du traitement. La fréquence des réactions était la plus élevée pendant les quatre premières années d'existence.

2. Les réactions peuvent être classifiées comme *légères* (affection catarrhale et/ou température subfébrile), de *gravité moyenne* (essoufflement asthmatic avec ou sans température subfébrile et affection catarrhale) et *graves* (attaques d'asthme et/ou haute température). Les formes graves ont été plus fréquentes dans les réactions postérieures que dans la première.

3. Le délai dans lequel les réactions se sont manifestées a été en moyenne de 48 heures après l'injection.

4. L'administration répétée de doses excessives, sans considération même de réactions légères, peut produire un état asthmatique ou une élévation persistante de température.

5. Un cas avec issue fatale est rapporté, dans lequel le décès a probablement été causé par une injection de vaccin ne contenant que 2 600 bactéries chez un sujet d'un an qui n'avait auparavant montré qu'une très faible réaction à la même dose. Ce cas et d'autres (qui n'eurent pas d'issue fatale) démontrent que la sensibilité des sujets au vaccin bactérien peut varier beaucoup et indiquent l'importance d'une surveillance sévère et d'un dosage très prudent des vaccins bactériens chez les sujets souffrant d'asthme.

6. Les réactions après les extraits allergènes «proprement dits» peuvent varier beaucoup plus qu'après les vaccins bactériens. Les premières sont en outre fréquemment des réactions immédiates, les secondes des réactions plus tardives.

7. Les réactions universelles de nature asthmatique qui suivent fréquemment même les petites doses de vaccin bactérien appuient la supposition de la présence chez ces enfants d'une allergie aux bactéries, aux produits de décomposition des bactéries ou aux substances produites par les mesures défensives de l'organisme contre les bactéries.

### **Zusammenfassung**

1. Von 162 asthmatischen Kindern, die mit einem Vaccin von gewöhnlichen pathogenen Bakterien der oberen Respirationswege behandelt wurden, wurden 63 allgemeine Reaktionen bei 42 Patienten (26 %) observiert; 24 (15 %) zeigten eine allgemeine Reaktion nach der ersten Dosis, während 33 (20 %) nach späteren Injektionen ein- oder mehrmals reagierten. Die höchste Reaktionsfrequenz zeigten Kinder unter 4 Jahren.

2. Die Reaktionen können eingeteilt werden in *leichte* (katarthaler Zustand und/oder subfebrile Temperatur), *mittelschwere* (asthmatisches Keuchen mit/oder ohne subfebrile Temperatur und Katarrh) und *schwere* (Asthma-Anfälle und/oder hohes Fieber). Schwere Formen traten häufiger bei späten Reaktionen auf als nach der ersten Injektion.

3. Eine Reaktion trat durchschnittlich 48 Stunden nach der Injektion ein.

4. Wiederholte Überdosierung ohne Rücksicht auf auch leichte Reaktionen kann einen Status asthmaticus oder eine langdauernde Fieberreaktion auslösen.

5. Ein tödlich verlaufener Fall wird mitgeteilt. Der Tod wurde wahrscheinlich durch Injektion eines Vaccines mit nur 2,600 Bakterien in ein einjähriges Kind verursacht, das früher auf dieselbe Dose nur ganz schwach reagiert hatte. Dieser Fall sowie andere (nicht tödlich verlaufene) zeigen, dass die Empfindlichkeit der Patienten gegen bakterielle Vaccine in hohem Grade wechseln kann und dass die Asthmapatienten genau zu überwachen sind und das Vaccin sehr vorsichtig dosiert werden muss.

6. Die Reaktionen auf „genuine“ allergene Extrakte kann in noch höherem Grade als auf bakterielle variieren. Die erstgenannten sind ausserdem oft unmittelbare Reaktionen, während die letzteren spätere sind.

7. Die universellen Reaktionen, die selbst nach kleinen Dosen von bakteriellen Vaccinen oft vorkommen, stützen die Annahme einer bei solchen Kindern vorhandenen Allergie gegen Bakterien, gegen deren Zerfallsprodukte oder gegen Substanzen, die durch die Abwehr des Organismus gegen die Bakterien produziert werden.

### Resumen

1. De 162 niños asmáticos tratados con vacuna de bacterias patogénicas ordinarias de la región respiratoria superior, han sido observadas 63 reacciones universales en 42 individuos (26 %); 24 (15 %) han reaccionado a la primera dosis, mientras que 33 (20 %) han tenido una o varias reacciones posteriores en el curso del tratamiento. La más elevada frecuencia de las reacciones era durante los cuatro primeros años de edad.

2. Las reacciones pueden clasificarse como *ligeras* (afección catarral y/o temperatura subfebril), de *gravedad media* (sofocación asmática con o sin temperatura subfebril y afección catarral), y *graves* (ataques de asma y/o alta temperatura). Las formas graves han sido más frecuentes en las reacciones posteriores que en la primera.

3. El tiempo medio en que las reacciones se manifestaban ha sido de 48 horas después de la inyección.

4. La administración repetida de dosis excesivas, sin consideración de reacciones ligeras, puede producir un estado asmático o una elevación persistente de la temperatura.

5. Un caso con desenlace fatal, en el cual se ha originado el fallecimiento probablemente por una inyección de vacuna que contenía sólo 2.600 bacterias en un sujeto de un año que no había mostrado antes más que una débil reacción a la misma dosis. Este caso y otros (que no fueron de consecuencias fatales) demuestran que la sensibilidad de los sujetos a la vacuna bacteriana puede variar mucho e indica la importancia de una supervigilancia severa y de una dosis muy prudente de vacuna bacteriana en los sujetos que padecen asma.

6. Las reacciones tras los extractos alérgenos «genuinos» pueden variar mucho más que después de las vacunas bacterianas. Los primeros son además con frecuencia reacciones inmediatas, los segundos reacciones más tardías.

7. Las reacciones universales de naturaleza asmática que siguen frecuentemente a las pequeñas dosis de vacuna bacteriana apoyan la suposición de la presencia en los niños de una alergia a las bacterias, a los productos de descomposición de las bacterias o a las sustancias producidas por las medidas defensivas del organismo contra las bacterias.

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## **The Effects of Adrenocorticotrophic Hormone (ACTH) in a Case of Juvenile Rheumatoid Arthritis<sup>1,2</sup>**

By

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It has long been known that remissions may occur in the course of rheumatoid arthritis. Several remedies have been found to induce remissions, especially gold salts. Transient improvement has been observed during starvation, after febrile reactions to foreign protein, after surgical operations (not only after removal of focal infections) and above all in the course of hepatitis and in pregnancy, where a remission frequently starts in the 4th to 6th week and ceases about one month after delivery, irrespective of the duration of the lactation.

These observations seem to be inconsistent with the theory that rheumatoid arthritis is a chronic infection and rather suggest the existence of some basic biochemical or hormonal disturbances (for further discussion and references, see HENCH, 1949).

HENCH, KENDALL and their collaborators have studied the effects of various hormones on the course of rheumatoid arthritis, and they found that Kendall's compound E, a steroid hormone from the adrenal cortex, had a noticeable effect (HENCH, KENDALL, SLOCUMB and POLLEY, 1949).

<sup>1</sup> A preliminary report was delivered by J. Vesterdal to the Danish Pediatric Society, Nov. 2, 1949.

<sup>2</sup> Supported by a grant from The National Danish Association against Rheumatic diseases.

The hormones of the adrenal cortex can be classified in three main groups:

1) *The mineralocorticoids* (desoxycorticosterone and others) which regulate the plasma electrolytes, causing a retention of Na and Cl and an excretion of K.

2) *The glucocorticoids* (corticosterone, 17-hydroxy-11-dehydrocorticosterone (= "Cortisone" = Kendall's compound E), 17-hydroxycorticosterone (= Kendall's compound F) and 11-dehydrocorticosterone). These steroids influence the intermediary metabolism of proteins, fat and carbohydrates (the blood sugar and the glycogen content of the liver are increased owing to stimulation of the conversion of amino acids into glucose). They increase the excretion of uric acid, and they also influence the blood-forming tissues, causing an atrophy of the lymph nodes and the thymus as well as a decrease in the number of circulating eosinophils. A decrease of short duration in the number of circulating lymphocytes has also been reported (see THORN & BAYLES, 1949).

3) *Sex hormone-like steroids* (oestrone, progesterone and androgenic substances) some of which cause nitrogen retention and exert oestrogenic or androgenic effects. Some of these hormones are 17-ketosteroids. (In children and adult females the urinary 17-ketosteroids are solely of adrenal origin, while in adult males they are produced by the testes as well as by the adrenal cortex.)

The steroids which, according to HENCH and his collaborators, are effective in rheumatoid arthritis belong to the glucocorticoid group. These researchers found that daily injections of 100 mg of compound E brought about a marked clinical improvement after a few days, and the sedimentation rate decreased from very high values almost to the normal in two to three weeks. The symptoms reappeared two to four days after discontinuation of the treatment. The only subsidiary effects of the treatment were a retention of water (2 to 3 kg in a few days), slight edemata, rounding of the facial contours and bradycardia. Slight hirsutism might occur.

A similar effect on rheumatoid arthritis was obtained by injection of the adrenocorticotrophic hormone (ACTH) of the anterior lobe of the pituitary gland.

Preparations of this hormone stimulate the production of all three groups of adrenal hormones. The active part of the ACTH molecule is a peptide consisting of about eight amino acids. (LI, 1949.)

In ACTH therapy, effects resulting from the increased pro-

duction of glucocorticoids are observed, as well as subsidiary effects from the increased production of sex hormone-like steroids and possibly also of mineralocorticoids. ACTH sometimes causes hypertension and in prolonged treatment a mild Cushing syndrome may appear.

The observations of HENCH & *al.*, 1949, have been confirmed by other investigators (ROBINSON & *al.*, 1949, THORN & *al.*, 1949, WOLFSON & *al.*, 1949, RAGAN & *al.*, 1949, TRAEGER & *al.*, 1949, BERGLUND & *al.*, 1949, and BRÖCHNER-MORTENSEN & *al.*, 1949).

During ACTH therapy a hypertrophy of the adrenal cortex will develop.

After intravenous injection ACTH disappears in about 5 minutes, as it is rapidly destroyed in most tissues (LI, 1949).

In Södra Sjukhuset in Stockholm a 4 year old child with rheumatoid arthritis was treated with ACTH, but almost without effect (E. JOHNSON & *al.*, personal communication). Perhaps this is due to antagonism between the growth hormone and ACTH (LI, 1949), or to immaturity of the adrenal cortex.

#### Authors' investigations

The ACTH preparations ("Cortrophin") were supplied by Nordiska Organon Inc., Stockholm, by the courtesy of Dr. Frederik Paulsen. The first preparation used was from the same batch as employed by BRÖCHNER-MORTENSEN & *al.*, 1949, who reported the strength of the preparation. Two other batches of "Cortrophin" were used after Nov. 9 resp. Nov. 24.

The dosage (in mg) refers to the Armour Standard.

#### Case record

J. M. D., J. no 321/49, a 10 year old girl, daughter of healthy parents, third of 3, one of whom died from a leucosis, the other one healthy.

Her arthritis started at the age of 1 1/4 years and was at first considered rheumatic fever. The heart was enlarged, but there were no electrocardiographic abnormalities. The arthritis stopped but reappeared one year later, and from the age of 2 1/2 years she was admitted on this account to various hospitals several times for long periods. The course was intermittent, with periods of well-being alternating with periods of high irregular fever and with joints involved, these sometimes lasting for



Fig. 1. The patient before treatment.

several months. Three times the disease relapsed after suppurative otitis. In 1947 mastoidectomy was performed on suspicion of sinusthrombosis, which was not confirmed. Tonsillectomy was performed in 1948.

The present admission to the Pediatric Department of Rigshospitalet, Copenhagen, was in April 1949. The first days she was very ill with high fever and gastric dilatation which was treated with gastric lavage, intravenous serum infusion and penicillin. She got a pericarditis which gradually healed. The fever remained high and irregular till June 1949. The hemoglobin decreased to 40 % and then a slow increase was seen during liver and iron therapy.

Gold salt therapy was administered at three of the admissions. The last time was during the present admission. It was discontinued on Sept. 14 1949. There was but little effect on the joints. The sedimentation rate was slowly decreasing (July 18: 122 mm/1 hr, Aug. 15: 100 mm and Sept. 19: 80 mm — measured by the Westergreen technique).

Examination of the patient at the start of the treatment (Fig. 1): The girl was very emaciated (weight 17.8 kg), of normal height, very pale, severely invalidated with capsular swelling and limited motion of all the joints of the extremities except the toe and distal finger joints. There were contractures of the elbows, hip joints and knees. The muscles of the extremities were extremely atrophic. She cried at the least attempt



Fig. 2. The patient after 3 weeks' treatment.

at passive motion of the joints involved. She lay almost motionless in the bed and could not be put into sitting position. She was almost unable to play with her toys.

The lymph nodes were moderately enlarged, but there was no splenomegaly. The heart was found somewhat enlarged on X-ray examination, and a systolic murmur was heard with maximum over the apex. Ophthalmological examination revealed nothing abnormal. The Wassermann reaction was negative, as also the tuberculin reaction. The antistreptolysin titer and the streptococcus agglutination titer were normal. The urine contained no sugar or protein and nothing abnormal on microscopical examination.

#### The ACTH treatment

The treatment started on Sept. 26 with 25 mg daily, divided into 4 intramuscular injections. The physical therapy was stopped.

Three hours after the first injection she could clasp her hands, and 6 hours later she was able to sit in semi-erect position. The next day the tenderness of the joints had almost completely disappeared, and she could sew and sit for a short time in a chair without pain. In the next few days the capsular swelling dimin-

ished considerably. After three weeks treatment she could ride a tricycle (Fig. 2). The lymph nodes diminished and disappeared completely after 19 days' treatment. In a few days her condition improved, she got a good appetite and her weight increased by 2.4 kg in the first week. Later the gain of weight was more slow.

The dosage was gradually diminished to 8–10 mg per day (see lower part of Fig. 3) without recurrence of the symptoms. 50 mg ACTH were given on Oct. 12 (to study the reaction of the adrenal cortex). The next day a slight palpebral edema appeared, but it only lasted for a few days.

After this she got only 4 mg per day without recurrence of the symptoms. On Oct. 17 she caught a cold, and simultaneously she got pains and tenderness of the knees and elbows, which were red and swollen. These joint symptoms disappeared after 4 days' treatment with 4 mg ACTH daily.

From Oct. 21 she got only 2 injections per day. The dosage was diminished to 1 mg per day, which was obviously too little, and in the next 24 days 2 mg per day were given. In this period there were only slight and transient pains in various joints, mainly around the left hip joint on account of fibrositis in the flexors of the hip.

On Nov. 17 the temperature rose to 38° C, and the joint symptoms recurred. As this was thought to be due to a pharyngitis, penicillin treatment was administered, but it was discontinued 4 days later, as no effect was seen.

From Nov. 24, 25 mg ACTH was given daily, divided into 3 daily injections, and after four days the dosage was gradually diminished to 5 mg per day, (divided into two daily injections). This time there was only a rather poor response to the treatment. The fever and the joint complaints recurred on Dec. 1. The laboratory findings did not show any effect of the agent. The treatment was discontinued on Dec. 10.

#### Laboratory findings

Most of the methods employed by us for studying the blood chemistry and the hormones in the urine are identical with those used by BRÖCHNER-MORTENSEN & *al.*, 1949.

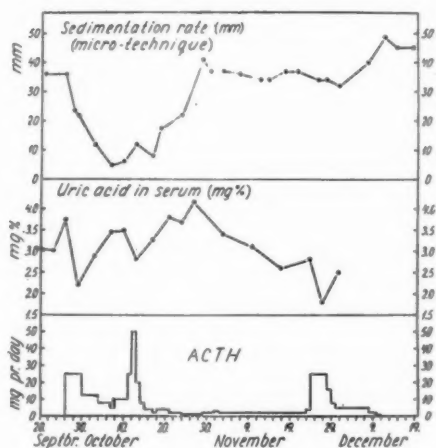


Fig. 3. Sedimentation rate (Landau's micro technique) and uric acid in serum.

The *sedimentation rate* (determined by the microtechnique of LANDAU, 1933) decreased from high values (36 mm/l hr) to the normal after 11 days' treatment, (Fig. 3). It increased again and again reached the initial value about 19 days later. There was no decrease during the last period of high dosage.

The *serum proteins* (fig. 4), determined by the biuret method of LEHMANN, 1944, decreased during the first period of the treatment and this was mainly due to a decrease of the globulins.

Electrophoretic examination of the serum proteins was performed in a Tiselius apparatus equipped with the Philpot-Svensson optic.

The serum was dialyzed for at least 48 hours against a buffer solution (phosphate, ionic strength 0.1, +sodium fluoride, ionic strength 0.1, total ionic strength 0.2, pH 7.7). The serum was then diluted with buffer solution to a protein content of about 1.3 %. The temperature of the thermostat was 0.5° C, and the experimental period averaged five hours. The potential gradient was about 5.5 volts/cm.

The separation of the different components on the electrophoresis diagram was made by the method of TISELIUS & KABAT, 1939, except the separation of albumin and alpha globulin which was made by aid of a symmetrical construction of the albumin peak. The relative concen-

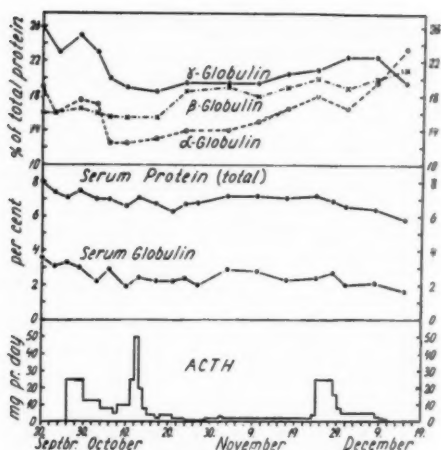


Fig. 4. Relative concentrations of  $\alpha$ ,  $\beta$  and  $\gamma$  globulin (determined by electrophoresis) and total protein and globulin (biuret method of Lehmann).

tration of gamma globulin was derived from the descending patterns only; all the other components were averages from both limbs after the ascending gamma globulin and the total area had been reduced with a value which made the ratio gamma globulin (ascend.)/reduced total area (ascend.) equal to gamma globulin (descend.)/total area (descend.). In this way our gamma globulin values contained only a salt gradient, but no delta protein gradient.

After 10 days' treatment with ACTH a normalisation of the serum protein pattern was seen (fig. 4), which means a relative increase of the serum albumin and a decrease of the alpha and gamma globulins. After 30 days' treatment a slow return to the initial values was seen.

The separation of  $\alpha_1$  and  $\alpha_2$  was difficult, but it seemed from the electrophoretic patterns that only  $\alpha_1$  changed while the alterations of  $\alpha_2$ ,  $\gamma_1$  and  $\gamma_2$  were relatively small.

The plasma fibrinogen was on Oct. 17 0.36 % and in the following weeks it increased slowly to very high values (0.83 %).

The hemoglobin increased during the first part of the treatment (fig. 5) and decreased during the last part. The anemia was slightly hypochromic, and the red blood count followed the hemoglobin value.



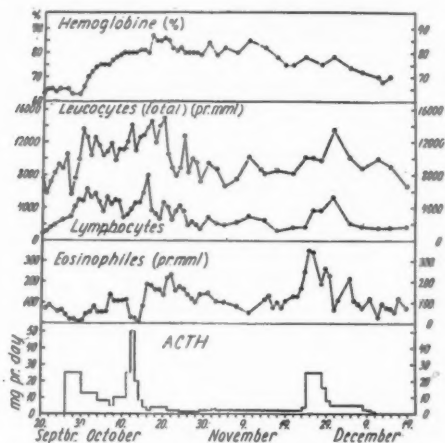


Fig. 5. Hemoglobin, white blood count and total number of lymphocytes and eosinophils.

During the treatment, the *white blood count* increased (fig. 5) as well as the number of circulating lymphocytes. The number of circulating eosinophils decreased from app. 75 almost to zero during the first period of high dosage (fig. 5) but it increased during the last period during which large doses had only small clinical effect.

The *serum potassium, sodium, calcium and chloride* as well as the *blood cholesterol* (determined by the micro method of LUNDSTEEN & VERMEHREN, 1936) and *alkaline phosphatase* (determined by the micro method of SCHOENHEIMER & SPERRY, 1934) showed no characteristic variations (fig. 6).

The concentration of *uric acid* in serum was slightly depressed when high doses of ACTH were given (fig. 3).

The *fasting blood sugar* varied irregularly during the first 9 days. The maximal value was 168 mg %. Glucose tolerance test performed before the treatment and on Oct. 15 was normal.

The content in serum of *non-specific inhibitor of hyaluronidase* (bovine testis hyaluronidase) was examined by the turbidimetric method of MEYER, 1947, and was found to decrease during the

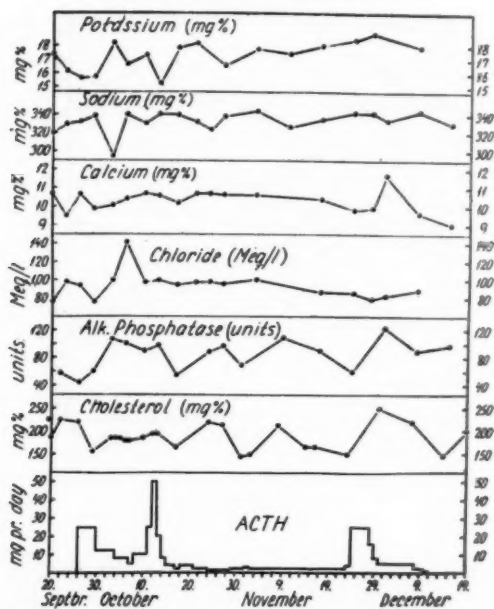


Fig. 6. Serum potassium, sodium, calcium and chloride, blood phosphatase (Lundsteen & Vermehren units) and blood cholesterol.

first period of high dosage (fig. 7). Serum did not inhibit streptococcal hyaluronidase (Lancefield's group A). A more thorough report of these observations has been published by FABER & SCHMITH, 1950.

The plasmin, plasminogen and antiplasmin concentration in citrated plasma was examined by T. ASTRUP, PH. D., but the preliminary investigations showed no definite differences from the normal.

The daily output of potassium, sodium, calcium and chloride in the urine increased during the treatment, but this was mainly because the child could not be kept on the standard diet owing to her great increase of appetite (the diet had to be supplemented by potatoes and bread). There were no characteristic variations of the excretion of creatine, creatinine and uric acid.

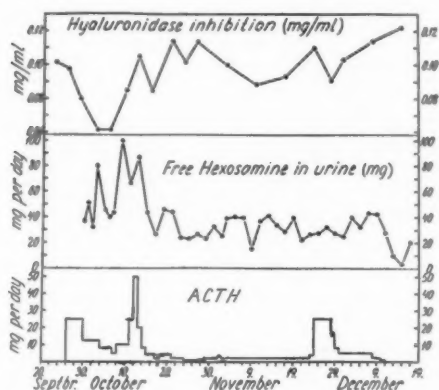


Fig. 7. Hyaluronidase inhibition (mg hyaluronidase inhibited per ml serum) and excretion of free hexosamine in the urine.

The excretion of *17-ketosteroids* is seen in fig. 8. It increased considerably after high doses of ACTH, also during the last period of high dosage, in contrast to the poor clinical effect.

The excretion of *glucocorticoids* varied in a similar manner. During the administration of 25 to 50 mg doses of the first batch of ACTH the reducing corticoids increased from 0.36 to 5.49 mg per 24 hours. During the last period of high dosage the maximal excretion, however, was only 1.55 mg per 24 hours. Further details are published by SPRECHLER, 1950.

The urine contained a little *sugar* on Oct. 13, but was otherwise free from sugar.

As stated earlier, there was no proteinuria before the treatment. On Oct. 6 *proteinuria* was found (0.2 ‰), which continued without any correlation to the ACTH treatment and is still present. The protein output increased considerably, the maximal value being 9 g per day. By microscopical examination of the urine a few casts were found, but no erythrocytes. The blood urea was not increased and there was no hypertension.

The daily output of free *hexosamine* in the urine was determined by the method of SØRENSEN, 1938, the analyses being performed on the urine without preceding hydrolysis. The results

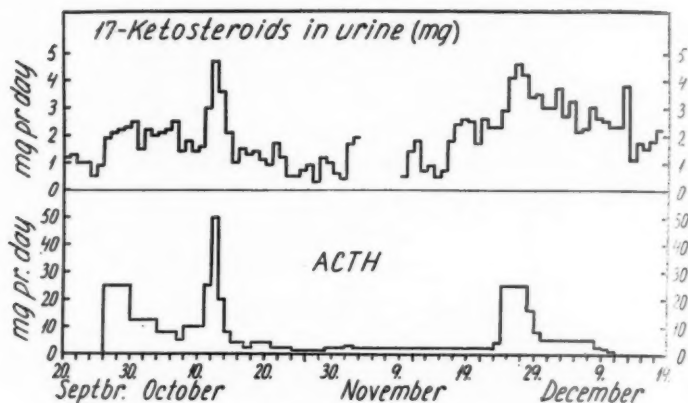


Fig. 8. Excretion of 17-ketosteroids in urine.

are seen in fig. 7. The excretion seems to be increased during the first part of the treatment.

The nitrogen balance was studied during the first part of the treatment (until Oct. 30). It was found to be slightly negative during the first ten days of the treatment, but the differences were not significant.

There were no changes in the electrocardiogram during the treatment, except that the  $T_3$  wave, which was negative before the treatment, became isoelectrical.

The calcium content of the bones (by X-ray examination) was constant.

The blood pressure was not significantly increased.

The pulse rate decreased from app. 90 to app. 70 during the treatment.

The size of the heart (by X-ray examination) was not influenced.

### Discussion

The girl was treated for a period of 76 days. The total dose was 572 mg, the daily dose varying between 50 mg and 1 mg.

The clinical improvement of the patient during the first part of the treatment was very remarkable and similar to that reported

by others. It was possible to maintain a rather good condition for almost a month with a very small dosage (2 mg per day), although the sedimentation rate rose to high values in this period.

A pharyngitis occurred in this period and caused joints to be involved, this disappearing after four days.

There were no signs of disorders in the electrolyte metabolism.

During the first period of high dosage a great increase of the output of 17-ketosteroids and glucocorticoids was seen.

During the last period of great dosage the condition improved little and a relapse was seen immediately after diminishing the dosage to 5 mg per day. This time a rather small increase of the excretion of glucocorticoids was seen, while the excretion of the 17-ketosteroids was as great as in the first period.

We have no explanation why the clinical effect was so poor in the last period, nor why a discrepancy between the excretion of the 17-ketosteroids and the glucocorticoids was seen. It must be noted that two different batches of ACTH were used in these periods.

The decrease of the non-specific hyaluronidase inhibitor in serum suggests that the effect of ACTH on connective tissue is exerted at least partly by a decrease of factors inhibiting hyaluronidase in the tissues, so that this enzyme may have a greater effect and break down the hyaluronic acid which causes the viscosity of the tissues. This is to some extent confirmed by our finding of a greater excretion of hexosamine (which is formed by depolymerisation of hyaluronic acid).

*The patient got a nephrosis during the treatment with ACTH,* and it is still present. Perhaps it is an amyloid nephrosis, which is not uncommon in children with rheumatoid arthritis, and which was brought out by the ACTH treatment.

#### Addendum

A new treatment with another batch of ACTH was administered on Jan. 12th—14th (50 mg daily for 3 days). This caused a long-lasting remission of the joint symptoms, but the treatment had to be discontinued because the edemata increased considerably. The sedimentation rate decreased from 41 to 16 mm (micro technique), and the eosinophils decreased to zero. There was a pronounced increase of the excretion of

both 17-ketosteroids and glucocorticoids. The hyaluronidase inhibitor in serum decreased to half of its initial value which was rather high. Electrophoretic examination of the serum proteins showed a nephrotic pattern with a low albumin content.

A congo red test was performed in Febr. 1950 (with the technique of TARAN and ECKSTEIN, *Am. J. Med. Sci.*, 203: 246, 1942) and indicated an amyloidosis (about 99 % absorption of the dye). From Dec. 30th she got a diarrhoea with voluminous yellow stools without demonstrable bacterial cause. It was at first considered a symptom of intestinal amyloidosis, but this diagnosis was abandoned as the stools contained blood, and the diarrhoea ceased two months later, whereafter the stools were normal.

### Summary

A 10 year old girl with a rheumatoid arthritis was treated with ACTH. At first a marked clinical improvement was seen as well as a decrease of the sedimentation rate to the normal. The treatment was continued with very small doses (2 mg daily) for a month. The sedimentation rate soon rose to the initial value, but a clinical relapse was not seen before the end of this period. A new treatment with high doses (but with another batch of ACTH) had only poor effect, and there was no decrease of the sedimentation rate.

After a few days' treatment she got albuminuria, and soon a severe nephrosis developed.

During the treatment the serum protein (particularly the  $\alpha_1$  globulin), the serum uric acid and non-specific hyaluronidase inhibitor in serum decreased. Hyperglycemia and glycosuria occurred to a slight extent. There were no significant alterations of serum K, Na, Ca, Cl, blood cholesterol, phosphatase, urea, plasmin, plasminogen or antiplasmin.

The hemoglobin, the white blood count and the number of circulating lymphocytes increased, while the eosinophils decreased.

There were no significant alterations of the nitrogen balance, nor in the excretion of creatine and creatinine. As to the excretion of K, Na, Ca and Cl, the results were inconclusive. The excretion of free hexosamine in the urine increased.

During the first period of high dosage the excretion of both

17-ketosteroids and glucocorticoids increased, but during the last period, when almost no clinical effect was seen, only the former increased.

### Résumé

Une fillette de 10 ans atteinte d'arthrite rhumatoïde a été traitée à l'ACTH. On a observé d'abord une amélioration clinique prononcée ainsi qu'une diminution du degré de sédimentation à la normale. Le traitement a été continué à très petites doses (2 mg par jour) pendant un mois. Le degré de sédimentation a bientôt augmenté jusqu'à sa valeur initiale, mais une rechute clinique n'a pas été observée qu'avant la fin de cette période. Un nouveau traitement à hautes doses (mais avec une autre quantité proportionnelle d'ACTH) n'a eu qu'un faible effet, et il n'y a pas eu de diminution du degré de sédimentation.

Après quelques jours de traitement, la malade a été atteinte d'albuminurie, et bientôt une grave néphrose se développa.

Pendant le traitement la protéine du sérum sanguin (particulièrement la globuline  $\alpha_1$ ), l'acide urique du sérum sanguin et l'antihyaluridase non-spécifique dans le sérum sanguin ont diminué. Il s'est produit dans une légère mesure de l'hyperglycémie et de la glycosurie. Il n'y a pas eu d'altérations significatives du sérum sanguin K, Na, Ca, Cl, du cholestérol sanguin, de phosphatase, d'urée, de plasmin, de plasminogène ni d'anti-plasmin.

L'hémoglobine, le nombre de globules blancs et le nombre de lymphocytes en circulation ont augmenté, tandis que les éosinophiles ont diminué.

Il n'y a pas eu d'altérations sensibles de la balance de nitrogène ni de l'excrétion de créatine et de créatinine. En ce qui concerne l'excrétion de K, Na, Ca et de Cl, les résultats ne permettaient pas de tirer de conclusions. L'excrétion d'hexosamine dans l'urine a augmenté.

Pendant la première période de haut dosage, l'excrétion de 17-kétostéroïdes et de glucocorticoïdes a augmenté, mais pendant la dernière période, alors que l'on n'a observé presque aucun effet clinique, seulement les premiers ont augmenté.

### Zusammenfassung

Ein 10-Jähriges Mädchen mit Rheumatoider Arthritis wurde mit ACTH behandelt. Im Anfang wurden eine entschiedene klinische Verbesserung und eine Verminderung der Senkungsgeschwindigkeit der roten Blutkörperchen auf die normale beobachtet. Die Behandlung wurde mit sehr kleinen Dosen (2 mg täglich) während eines Monats fortgesetzt. Die Senkungsgeschwindigkeit stieg bald wieder auf den ursprünglichen Wert. Ein klinisches Recidiv kam jedoch erst am Ende des Monats. Eine erneute Behandlung mit starken Dosen (jedoch mit einer anderen Sorte ACTH) hatte nur schwache Wirkung und die Senkungsgeschwindigkeit blieb hoch.

Nach mehrtätiger Behandlung trat Albuminurie auf, und bald entwickelte sich eine ernste Nephrose. Während der Behandlung sanken die Werte des Serumproteins (vor allem des  $\alpha_1$ -Globulins) der Serumurinsäure und des nichtspezifischen Antihyaluronidase im Serum. Eine leichte Hyperglykämie und Glykosurie wurde beobachtet, jedoch keine deutliche Veränderungen des K, Na, Ca, Cl, Cholesterin, Phosphatas, Urea im Serum oder des Plasmin, Plasminogen oder Antiplasmin.

Das Hämoglobin, die Zahl der weissen Blutkörperchen, die Zahl der Lymphocyten nahmen zu, während die Zahl der Eosinophilen sich verminderten.

Keine merkbaren Veränderungen des Eiweissumsatzes oder der Ausscheidung von Kreatin und Kreatinin wurden beobachtet. Die Resultate der Untersuchung über Ausscheidung von K, Na, Ca und Cl waren nicht aufschlussreich. Die Ausscheidung von freiem Hexosamin im Urin war gestiegen.

Während der ersten Behandlungsperiode mit starken Dosen trat eine gesteigerte Ausscheidung der 17-Ketosteroide und Glukokorticoide ein, während der letzten Periode, in der fast keine klinische Wirkung beobachtet wurde, trat dagegen nur eine Steigerung der Ausscheidung der erstgenannten ein.



### Resumen

Una muchacha de 10 años atacada de artritis reumatoide ha sido tratada con ACTH. Se ha observado primeramente una mejoría clínica pronunciada, así como una disminución de la velocidad de sedimentación a lo normal. El tratamiento se ha mantenido con tres pequeñas dosis (2 mg por día) durante un mes. La velocidad de sedimentación ha aumentado en seguida hasta su valor inicial, pero no se ha observado recaída clínica antes de acabar este período. Un nuevo tratamiento de altas dosis (pero con otra cantidad proporcional de ACTH) no ha ejercido más que un efecto débil y no ha habido disminución de la velocidad de sedimentación.

Después de algunos días de tratamiento la enferma ha sido atacada de albuminuria, y en seguida se desarrolló una grave nefrosis.

Durante el tratamiento, la proteína del suero sanguíneo (particularmente la globulina  $\alpha_1$ ), el ácido úrico del suero sanguíneo y la antihialurinidad no específico en el suero sanguíneo han disminuido. Se produce en una ligera proporción la hiperglicemia y la glucosuria. No ha habido alteraciones significativas del suero sanguíneo K, Na, Ca, Cl, del colesterol sanguíneo, de fosfatasa, de urea, de plasmín, de plasminógeno ni de antiplasmín.

La hemoglobina, el número de glóbulos blancos y el de linfocitos en circulación han aumentado, mientras que los eosinófilos han disminuido.

No ha habido alteraciones sensibles del balance de nitrógeno ni de la excreción de creatina y creatinina. En lo que concierne a la excreción de K, Na, Ca, y Cl, los resultados no permitían formular conclusiones. La excreción de hexosamina en la orina ha aumentado.

Durante el primer período de alta dosis, la excreción de 17-quetosteroides y de glucocorticoides ha aumentado, pero durante el último período, cuando no se ha observado casi ningún efecto clínico, solamente los primeros han aumentado.

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## **Quelques cas de méningite grippale traités par la streptomycine**

par

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La méningite grippale intéresse tout spécialement la pédiatrie étant donné que la grande majorité des cas (env. 83 %) concerne des enfants de moins de 3 ans (Fothergill 1937) et que la mortalité est très élevée au premier âge. Dans leur ouvrage «Traitement des méningites aiguës», Martin et ses collaborateurs donnent des chiffres de mortalité allant de 97 à 100 %, selon un rapport de Dana en 1939. En 1941 Grob a montré dans une statistique que la mortalité chez les enfants de moins de 2 ans était de 95,5 % avant l'emploi des sulfamides.

A partir de l'époque où Margareta Pittman (1931—33) eut montré que la plupart des souches dans la méningite grippale hém. appartiennent au groupe sérologique B, on a pu préconiser et appliquer une thérapeutique spécifique par l'immunsérum de cheval. Ce traitement fut proposé par ce même auteur et par Fothergill. Cependant, ce sérum ne semble pas avoir sensiblement diminué la mortalité. Ce n'est qu'avec la sulfamide que l'on obtint un remède capable de diminuer la mortalité dans la méningite de Pfeiffer. Depuis ces dix dernières années on a essayé de nombreuses combinaisons de médicaments spécifiques et la rapidité des changements n'a guère permis de se faire une opinion exacte. Des dérivés nouveaux et plus efficaces de la sulfamide sont apparus. Engbaeck (1948) a fait une statistique basée sur des publications anglosaxonnes essentielles sur les malades de plus de 7 mois traités par un dérivé de sulfamide. Il a trouvé une mortalité variant de 30 à 70 %. Sur 93 cas traités par Engbaeck lui-même par divers dérivés de la sulfamide, il ne put conclure à aucune dimi-

nution certaine de la mortalité. Hattie Alexander, au contraire, a de bons résultats depuis 1938. Elle a combiné la sulfamide et plus tard la sulfamide-pyridine et la sulfadiazine avec un sérum de lapin immunisé au type spécifique. Elle donne au départ une dose de sérum de 25 à 100 mg d'azote-anticorps selon la teneur en sucre du liquide céphalo-rachidien. Au cours du traitement, on contrôle la teneur du sérum du malade en anticorps (après l'avoir dilué 1:10). S'il n'y a pas d'agglutination, elle donne à nouveau une dose de 25 mg d'azote-anticorps etc. Selon une publication faite en 1944, Hattie Alexander avait 78 % de survivants sur un ensemble de 87 observations.

Smith Wilson et Hodes ont donné un rapport en 1946 sur 28 cas de méningite grippale hém. traités par une combinaison de sulfamide et de sérum de lapin, spécifique au type. La mortalité était de 14 % environ. Un petit nombre d'observations a été publié en 1948 par Engbaeck (1 malade de 5 mois, les 6 autres entre 7 mois et 5 ans): 2 malades sont morts (7 et 9 mois).

La pénicilline a trouvé un emploi très limité car si l'on a, comme Gordon et Zimmermann (1945), constaté que le type B y est sensible dans un grand pourcentage des cas, les résultats cliniques restent maigres, même en combinaison avec des sulfamides. (Zimmermann 1946.) En 1948, Martin se montre cependant favorable au traitement par la pénicilline, combiné à la sulfamide et présente 4 cas traités avec succès. D'autre part, l'on ne rencontre que quelques rares observations sur le traitement par la pénicilline et presque toujours combiné à la sulfamide.

On avait toujours une forte mortalité chez les enfants de moins de 7 mois (Alexander 1943), 80 %. Souvent, ils ne présentent pas les signes ordinaires de méningite et viennent ainsi très tard sous traitement. Il semble que l'on puisse fonder un grand espoir sur la streptomycine, éventuellement combinée à la sulfamide et au sérum de lapin. C'est surtout Alexander qui a étudié la grande sensibilité de la grippe hém. type B à la streptomycine. Au cours d'expériences portant sur des souris, l'effet protecteur obtenu vis-à-vis d'un certain nombre de germes de grippe hém. lors d'application de sulfadiazine, de sérum, de sérum et de sulfadiazine combinés et enfin de streptomycine fut respectivement de 1:3:

85: 10 000. Alexander a aussi montré l'accroissement énorme et rapide de la résistance qui apparaît dans les expériences comme en clinique.

Dans le tableau I j'ai réuni les résultats des cas dans lesquels la streptomycine a été employée avec le plus de pertinence. La plupart des malades avaient précédemment ou simultanément été traités par la sulfamide ou par le sérum ou par les deux. La mortalité totale s'élève ainsi à un peu plus de 10 %. Les malades décédés avaient presque tous moins de 18 mois. La moyenne de la mortalité a donc encore baissé grâce à la streptomycine. Voir le premier tableau.

Il est assez difficile de faire une comparaison valable de cette manière, car les cas traités par la streptomycine sont des cas particulièrement graves, qui n'ont pu être guéris par la sulfamide ou par le sérum. Chez la plupart des auteurs, les doses ont varié entre 25 000 et 100 000 u. i. par voie intralombaire par jour pendant une semaine et de 50 000 à 100 000 u. i. par voie intramusculaire par kg du malade et par jour, divisées en six piqûres, pendant 2 à 3 semaines (lgr = 1 000 000 u. i.). Alexander, qui a le plus d'expérience, s'est servi de 45 000 u. par kg du malade par voie intramusculaire et de 25 000 à 50 000 u. par voie lombaire pendant près d'une semaine. Elle met en garde contre une application trop prolongée, qui peut amener des lésions de l'appareil auditif ou du labyrinthe.

J'ai suivi les observations des méningites grippales hém. traitées par la streptomycine à la Clinique de Debré à l'Hôpital des Enfants Malades durant la période juillet 1947, où le premier cas fut traité, jusqu'à mars 1948.

Il s'agit de 12 malades, tous entre 6 et 18 mois, sauf un qui avait à peine 3 ans. La plupart avaient, les semaines avant l'admission, eu des otites, des pneumonies, des pyélites ou d'autres affections infectieuses. Souvent la méningite grippale avait été traitée un certain temps par la sulfamide ou par la pénicilline et la méningite se trouvait dans une phase subaiguë avec prédominance de cellules mononucléaires dans le liquide (par ex. les obs. 3 et 9). L'état général des malades à l'entrée en clinique était presque toujours très mauvais. Ce n'est qu'après des déplacements

Tableau I.

Age	Nombre de malades	Morts	Auteurs
< 1 an $\frac{1}{2}$ ...	3	—	NUSSBAUM et autres, 1946.
(< 7 mois ...	0	—)	
> 1 an $\frac{1}{2}$ ...	0	—	
< 1 an $\frac{1}{2}$ ...	4	—	LOGAN et HERREL, 1946.
(< 7 mois ...	0	—)	
> 1 an $\frac{1}{2}$ ...	0	—	
< 1 an $\frac{1}{2}$ ...	5	2	WEINSTEIN, 1946.
(< 7 mois ...	2	1)	
> 1 an $\frac{1}{2}$ ...	4	—	
< 1 an $\frac{1}{2}$ ...	13	2	ALEXANDER, 1947.
(< 7 mois ...	0	0)	
> 1 an $\frac{1}{2}$ ...	12	0	
*—	15	1	PAINE et FINLAND, 1947.
(< 1 an ....	10	?)	
< 1 an $\frac{1}{2}$ ...	16	3	BRUNS SLOT et autres, 1948.
(< 7 mois ...	4	1)	
> 1 an $\frac{1}{2}$ ...	3	2	
*—	22	2	LINDGREN et SJÖGREN, 1948.
< 1 an $\frac{1}{2}$ ...	5	1	ENGBAECK, 1948.
(< 7 mois ...	1	1)	
> 1 an $\frac{1}{2}$ ...	2	0	
< 1 an $\frac{1}{2}$ ...	8	2	HOYNE et BROWN, 1948.
(< 7 mois ...	2	1)	
> 1 an $\frac{1}{2}$ ...	10	—	
< 1 an $\frac{1}{2}$ ...	3	0	HAUGE, 1949.
(< 7 mois ...	1	0)	
> 1 an $\frac{1}{2}$ ...	5	0	
< 1 an $\frac{1}{2}$ ...	0	0	ÖBERG, 1949.
> 1 an $\frac{1}{2}$ ...	4	0	
Total < 1 an $\frac{1}{2}$	57	10	
» > 1 an $\frac{1}{2}$	40	2	
Total	97 (134)*	12 (15)*	

\* En ce qui concerne les chiffres entre parenthèse, les informations des deux publications où l'âge des malades n'était pas indiqué, y sont compris.

plus ou moins longs qu'ils ont pu être admis à l'Hôpital des Enfants Malades, qui a fait fonction de centre de streptomycine.

La dose intramusculaire de streptomycine a varié entre 50 000 et 100 000 par kg et par jour. La durée de l'application intramusculaire a été de 2 à 4 semaines dans les cas guéris. La dose intralombaire a généralement varié entre 40 000 et 100 000 u. i. durant 1 à 2 semaines. Dans le premier cas, où l'on manquait encore d'expérience, la dose intralombaire de streptomycine fut très élevée, 100 000  $\times$  2 par jour. Les derniers cas ont reçu une dose intralombaire relativement petite. Parfois la streptomycine a été appliquée par voie intraventriculaire, surtout à la moindre crainte d'occlusion. Dans 2 cas il a été donné jusqu'à 100 000 u. i. par voie intraventriculaire et cela semble avoir provoqué un choc. Si l'on désire appliquer la streptomycine par voie intraventriculaire, il paraît préférable de donner des doses moindres. 24 heures après le début de l'application de la streptomycine, on ne pouvait plus déceler de germes dans le liquide céphalo-rachidien. Dans quatre cas (4, 5, 6, et 10) le traitement par la streptomycine a été combiné plus ou moins longtemps avec des sulfamides. La ventriculographie a été pratiquée dans presque tous les cas et surtout quand on soupçonnait tant soit peu une occlusion. La première observation montre l'importance qu'il y a à poursuivre le traitement assez longtemps. Le malade sortit après à peine 2 semaines de traitement à la demande des parents. Il revint 15 jours plus tard avec des signes d'hydrocéphalie, de cécité et une hémiparésie. L'hydrocéphalie fut confirmée par la ventriculographie. On fit une opération au cours de laquelle on établit une communication entre le 3ème ventricule et la citerne chiasmatique. Il est difficile de se prononcer sur l'importance de l'opération. Cependant la stase papillaire et les autres symptômes cédèrent. A l'occasion d'un contrôle un an plus tard à peu près, il y avait toujours une légère hydrocéphalie, mais par ailleurs l'état somatique et psychique n'avait rien de particulier.

Les malades sont décédés dans trois cas. Dans la 5ème observation, 8 mois, où le malade ne resta qu'un jour en clinique, une journée précieuse avait été perdue par le passage dans un autre hôpital. Dans la 2ème observation, 16 mois, la méningite durait de-

Tableau II.

Observation no.	Age en années	Jours de maladie avant l'entrée	Sulfam. avant l'entrée	Penic. avant l'entrée	Infect. précédant la méningite ou l'accomp. avant l'entrée	Etat gén. à l'entrée	Grippe h. dans le liq. (cult) à l'entrée	U. i. str. int.-musc. par kg et par jour (1 gr = 1 000 000 u. i.)	U. i. str. int.-lomb par jour	Sulfamide	Commentaire
1.	1 7/12	1 mois (?)	+	+	Pneumonie, pyélite	Peu altéré	+	60-100 000 pendant 10 jours	100 000 × 2 pendant 6 jours	—	Sorti à la demande des parents après 10 jours de traitement. Reçute au bout de 15 jours. Réadmis. Hydrocéphalie int. hémiparésie, stase papillaire. Opération et nouvelle application de streptomycine int.-m. Guérison progress. avec de légères séquelles.
2.	1 4/12	3-4 sem.	?	?	—	Coma	+	90 000 pendant 3 jours	100 000 pendant 3 jours	—	Sorti mourant à la demande des parents.
3.	6/12	3 jours	—	—	Bronchite	Coma	+	60-80 000 pendant 3 sem.	50-80 000 pendant 2 sem.	—	50-100 000 u. i. de streptomycine intraventriculaire, 1 j. sur 2, 6 fois. Quelques heures après l'injection un choc soudain bientôt dissipé. Sorti guéri.
4.	11/12	3 sem.	+	+	—	Peu altéré	+	50 000 pendant 2 sem.	50 000 pendant 2 jours	+	Sorti guéri.
5.	8 12	2 jours	—	—	—	Précoma	+	65 000 pendant 3 jours	50 000 pendant 2 jours	—	Mort de bouche ouverte l'abat-muscul.
6.	1 4/12	2 jours	—	—	Bronchite	Précoma	+	50 000 pendant 3 jours	25 000-50 000	+	Sorti guéri.



6.	1 4/12	2 jours	—	—	Bronchite	Précoma	+	50 000 pendant 3 sem.	25 000— 50 000 pendant 20 jours	+	Sorti guéri.
7.	1	2 jours	—	—	Otite	Très altéré	+	55-85 000 pendant 4 sem.	25-50 000 pendant 12 jours	—	Sorti guéri.
8.	9/12	4-5 sem.	+	+	Gastro- entérite	Très altéré	—	50-75 000	50 000 pendant 1 sem.	—	2 sem. après l'adm. la ventriculographie déce- lait une dilatation moyenne des ventricules. Aucune hydrocéphal. clin. Sorti guéri.
9.	8/12	2 sem.	+	+	—	Très peu altéré	+	70 000 pendant 4 sem.	25-50 000 pendant 9 jours	—	Sorti guéri.
10.	1	1 sem.	+	+	—	Très altéré	+	45-90 000 pendant 4 sem.	15-30 000 pendant 9 jours	+	Exanthème toxyue dû à la streptomycine. Sorti guéri.
11.	11/12	2 jours	—	+	Le mois préc. mastoidite, toxicoose, bronchop- neum	Coma	+	100 000 pendant 5 jours	15-21 000 × 2 pend. 5 jours	+	A l'entrée, la méningite se compl. d'un abcès sous la duremère qui fut traité localement par 15 000 u. i. chaque jour. Malgré une amél. init., le malade est mort le 6ème jour.
12.	2 10/12	3 jours	+	+	—	Précoma	+	60-80- 100 000 p. 3 sem.	50-80- 100 000 p. 2 sem.		On soupç. une occlus. malgré un fond d'œil normal, mais une trep. en vue d'une ponc. ventr. n'a rien décelé. 10 000 u. i. pend 3 jours. Réapparit. de fièvre, exanthème, et raideur de la nuque dus à la streptomycine.

puis plusieurs semaines et se trouvait dans une phase subaiguë avec un très mauvais état général à l'entrée. La malade n° 11, 11 mois, était aussi dans un état subaigu avec un abcès sous la dure-mère. Dans tous ces cas les possibilités de guérison étaient minimes. Parmi les autres, un a été hydrocéphale comme il a été dit plus haut. A cette exception près, il semble qu'il ne soit pas resté de signes cliniques attribuables à la méningite ou à la streptomycine. (Les malades n'ont pas été régulièrement contrôlés par un otollogue.) Un petit nombre de cellules mononucléaires et un léger accroissement de l'albumine dans le liquide céphalo-rachidien ont pu être relevés pendant quelques jours après la fin de l'application intralombaire de streptomycine. Ce phénomène doit probablement être attribué à une irritation due à la streptomycine.

Etant donné la grande mortalité dans la méningite grippale à ces âges ainsi que les autres circonstances défavorables décrites ci-dessus, on peut considérer que les résultats sont bons. En appliquant la streptomycine dès le début et en la combinant régulièrement avec de la sulfamide et dans certains cas spécialement difficiles avec du sérum selon Alexander, la mortalité doit pouvoir être encore réduite. Ceci est d'autant plus probable qu'Alexander a eu de si bons résultats avec son sérum dans adjonction de streptomycine.

### Resumé

L'auteur a étudié 12 cas de méningite grippale hém. dont 11 entre 6 et 18 mois. Ces cas ont été traités en 1947—48 par la streptomycine intramusculaire (50—100 000 u. i. par kg et par jour, divisées en 6 doses, 2—4 semaines) et intralombaire (40—100 000 u. i. par jour, 1—2 semaines). Là où il y avait crainte d'occlusion, la streptomycine a été donnée par voie intraventriculaire, ce qui semble avoir provoqué une certaine irritation dans les fortes doses. Trois malades sont morts (entre 8 et 16 mois). Description d'un cas d'hydrocéphalie int. qui subit une intervention neurochirurgicale et qui évolua favorablement. Aucune suite n'a été constatée chez les autres malades, ni de la méningite ni du traitement avec la streptomycine.

**Summary**

The author has studied 12 cases of meningitis influenzal haem., 11 of them between 6 and 18 months. These cases were treated in 1947—48 by intramuscular streptomycin (50—100 000 u. i. per kg and per day, divided in 6 doses, 2—4 weeks) and intrathecally (40—100 000 u. i. per day, 1—2 weeks). Where there was fear of occlusion the streptomycin was administered intraventricularly, which as regards the strong doses appears to have provoked a certain irritation. Three of the patients died (between 8 and 16 months). A case of hydrocephalus in. which was submitted to neuro-surgical intervention is described which had a favourable course. No complications were observed in the other patients, neither of the meningitis, nor of the treatment with streptomycin.

**Zusammenfassung**

Verfasser hat 12 Fälle von Influenza-Meningitis untersucht, davon 11 im Alter von 6—18 Monaten. Diese Fälle wurden 1947—48 mit Streptomycin behandelt und zwar 50—100 000 Einh. per Kg und Tag in 6 Dosen geteilt, während 2—4 Wochen und 40—100 000 Einh. intralumbal täglich während 1—2 Wochen. Bei Oclusionsverdacht wurde das Streptomycin intraventrikulär gegeben, was bei der hohen Dosierung eine gewisse Reizung hervorrief. Drei der Patienten starben (8—16 Monate alt). Ein Fall von Hydrocephalus int. wird beschrieben welcher nach einem neuro-chirurgischen Eingriff einen günstigen Verlauf nahm. Sonst wurde keine Komplikationen, weder auf Grund der Krankheit oder der Behandlung beobachtet.

**Resumen**

El autor ha estudiado 12 casos de meningitis gripal hem., de los cuales once estaban comprendidos entre 6 y 18 meses. Estos casos han sido tratados en 1947—48 con estreptomicina intramuscular (50—100 000 u. i. por kilo y por día, divididas en 6 dosis, 2—4 semanas) y por vía intralumbar (40—100 000 u. i. por día, 1—2 semanas). Donde había temor de oclusión la estreptomicina ha sido administrada por vía intraventricular, lo que pareció haber provocado cierta irritación al aplicar dosis fuertes. Tres enfer-

mos han muerto (entre 8 y 16 meses). Descripción de un caso de hidrocefalia int. que sufrió una intervención neuroquirúrgica y que evolucionó favorablemente. Ningunas consecuencias han sido comprobadas en los otros enfermos, ni de la meningitis ni del tratamiento con estreptomycin.

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FROM THE PEDIATRIC CLINIC OF THE CAROLINE INSTITUTE AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL AND THE IV-TH MEDICAL  
SERVICE OF ST. ERIK'S HOSPITAL, STOCKHOLM.

## **Evaluation of the effect of d-amphetamine sulfate in the treatment of obesity in children<sup>1</sup>**

by

**HANS-OLOF MOSSBERG and A. RUNE FRISK**

Obesity results from the ingestion of more food than is utilized. The important part played by psychic factors in the development of overweight both in adults and in children is being more and more stressed (1, 2, 3, 4, 5). Treatment of the patient should primarily be based on an understanding of the psychologic reasons for his overeating, but the use of anorexigenic drugs helps the patient to keep to a prescribed regimen. The appetite-depressing effect of amphetamine sulfate was soon noticed and this compound has been widely used as a supplementary aid in the treatment of obesity (for literature see HARRIS et al (6)). This drug, however, proved to be unsatisfactory in many patients because of certain undesirable symptoms which it produced. The dextroisomer, d-amphetamine sulfate, on the other hand, effectively suppresses the desire for food without producing any undesirable effects from the central nervous system. In animal experiments the appetite-depressing effect of this drug is twice that of the racemic compound (6), amphetamine sulfate, and clinical experience supports the view that d-amphetamine sulfate is the drug of choice (4, 5, 7, 8). In order to estimate the anorexigenic effect of this compound in a more quantitative way the following study was made. In a group of unselected obese children, whose ages ranged from 7 to 15 years, besides food restrictions every other child was given

<sup>1</sup> The d-amphetamine sulfate (afatin) and the placebo tablets were kindly placed at our disposal by Astra Laboratories, Södertälje, Sweden.

d-amphetamine sulfate and every other placebo tablets with the same dosage scheme. The weight loss for the two groups was then compared.

### Material.

The degree of overweight was expressed by means of Rohrer's index (9, 10). This index is fairly constant and at about the same magnitude for both normal girls and boys within an age range of 7 to 15 years (9). Within these age limits a comparison between different Rohrer indices therefore can be made without any correction, and the normal mean value for these age groups is found to be about 1.18 (9). Furthermore the result of the treatment is directly reflected in the decrease of Rohrer's index. In this study only obese children between the ages of 7 and 15 years are included.

In all, the material comprises 167 cases, 111 being girls and 56 boys. The group treated with d-amphetamine sulfate consists of 84 cases and the group to which placebo tablets was given of 83 cases. The number of boys was the same in both groups, the former containing 29 and the latter 27. The age distribution is given in table 1. As will be seen from the table it was about the same, and even, in the two groups; about 60 per cent of the cases were between 9 and 11 years of age.

Table 1.

Age distribution.

Age (years)	7	8	9	10	11	12	13	≥ 14	Total
d-amphetamine group . . . . .	7	11	13	17	14	12	7	3	84
Placebo group . . . . .	8	4	18	17	12	9	6	9	83
Total	15	15	31	34	26	21	13	12	167

Table 2 shows the degree of overweight in this material. A Rohrer's index of 1.30 to 1.55 corresponds to an overweight of

Table 2.

Overweight distribution. Number of cases.

Rohrer's index	1.30—1.55	1.56—1.80	> 1.80	Total
d-amphetamine group. . . .	19	50	15	84
Placebo group . . . . .	25	39	19	83
Total	44	89	34	167

10 to 30 per cent, one of 1.55 to 1.80 to 30 to 50 per cent and one exceeding 1.80 to a weight which is more than 50 per cent above the normal. Moreover an index of 1.55 represents the upper limit of the normal range of variation and thus 74 per cent of all cases had a weight above this limit. In 20 per cent of the material the weight was more than 50 per cent above the normal. The degree of overweight was the same both in the d-amphetamine and the control group.

#### Treatment.

All patients were untreated before, and they were in every instance handled as out-patients. In all cases restrictions in the food intake were prescribed. No special diet was used. A high protein, low fat and a low carbohydrate diet was aimed at, with no calculation of its caloric values. Irrespective of sex, every second patient was given tablets containing 2.5 mg of d-amphetamine sulfate 3 times daily before the main meals. The other patients were given placebo tablets in the same way. Both d-amphetamine sulfate and placebo tablets were of the same size and appearance, had the same taste and were packaged and labelled in exactly the same way. Only the physician, who also distributed all of the tablets, knew about the contents of the different packages. The patients were then controlled at regular intervals, in the beginning once a month and then at longer intervals, in no case exceeding three months. At this control the height and weight was recorded and both the child and the parents were reassured.

### Results.

The mean weight loss with this treatment for the whole material is given in figure 1. During the first 3 to 4 months the rate at which the weight was reduced was more rapid in the group treated with d-amphetamine sulfate than in the control group.

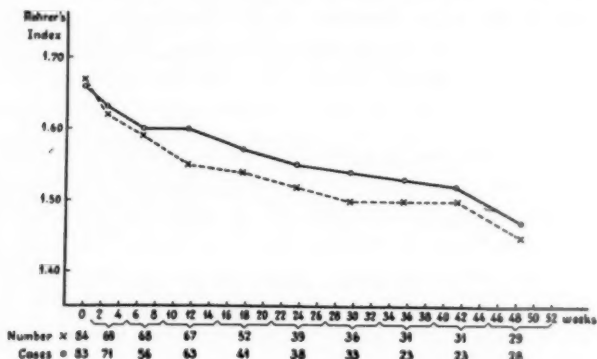


Fig. 1. Average weight loss for the whole material.

x = d-amphetamine sulfate group.

o = placebo group.

After that time the weight loss proceeded at about the same rate for both groups. The figures do not permit an accurate comparison of the effect of treatment in the two groups, for the following reasons. The time of observation was different for various patients, and in a given case the control examinations did not always fall within these periods of time, which had been chosen at random. Therefore no definite figures for the weight loss can be constructed from the curve. In order to determine the effect of the treatment for the two groups in an accurate way the differences in Rohrer's index for each period of time were calculated by statistical methods for the two groups (table 3). During the whole time of treatment there was for each period of time a higher weight loss in the d-amphetamine group than in the control group. These differences are statistically significant during the first five



Table 3.

Decrease in Rohrer's index.

Period of treatment, weeks	d-amphetamine group		Placebo group		Difference
	Number of cases	Mean	Number of cases	Mean	
1—4	69	$0.06 \pm 0.005$	71	$0 \pm 0.004$	$0.06 \pm 0.006$
5—8	68	$0.08 \pm 0.007$	56	$0.05 \pm 0.007$	$0.03 \pm 0.010$
9—14	67	$0.12 \pm 0.008$	63	$0.07 \pm 0.009$	$0.05 \pm 0.012$
15—20	52	$0.14 \pm 0.009$	41	$0.09 \pm 0.013$	$0.05 \pm 0.016$
21—26	39	$0.16 \pm 0.014$	38	$0.12 \pm 0.016$	$0.04 \pm 0.021$
27—32	36	$0.17 \pm 0.014$	33	$0.12 \pm 0.016$	$0.05 \pm 0.021$
33—38	31	$0.18 \pm 0.017$	23	$0.14 \pm 0.019$	$0.04 \pm 0.026$
39—44	31	$0.18 \pm 0.015$	23	$0.12 \pm 0.020$	$0.06 \pm 0.025$
45—52	29	$0.21 \pm 0.017$	28	$0.13 \pm 0.017$	$0.08 \pm 0.024$
53—65	28	$0.22 \pm 0.015$	24	$0.16 \pm 0.021$	$0.06 \pm 0.026$
66—78	19	$0.21 \pm 0.018$	13	$0.19 \pm 0.038$	$0.02 \pm 0.042$

months of therapy; thereafter, due to a decreasing number of observations, they are of varying degrees of probability. The individual weight loss for the patients who were treated and observed for from 45 to 52 weeks is given in table 4. In both groups there were patients who lost no weight during the observation

Table 4.

Decrease in Rohrer's index in patients treated and observed for 45 to 52 weeks.

Decrease in Rohrer's index	d-amphetamine group				Placebo group			
	Number of cases	Mean Rohrer's index			Number of cases	Mean Rohrer's index		
		Before	After	Diff.		Before	After	Diff.
$\leq 0.05$	1	1.52	1.48	-0.04	6	1.52	1.52	$\pm 0$
0.06—0.20	14	1.62	1.48	-0.14	15	1.59	1.45	-0.14
$> 0.20$	14	1.71	1.42	-0.29	7	1.72	1.48	-0.24
Total	29	1.66	1.45	-0.21	28	1.60	1.47	-0.13

time, and cases showing a considerable loss of weight, but the number of cases that reacted favorably to the treatment were greater in the d-amphetamine group.

The feeling of hunger and the appetite was also decreased more often in the group treated with d-amphetamine sulfate than in the placebo group (table 5).

Table 5.

Influence of the treatment upon the subjective feeling of hunger.

	d-amphetamine group. No. of cases	Placebo group. No. of cases
Unchanged .....	5	23
Less pronounced hunger feelings .....	18	22
No hunger feelings .....	33	11

Any ill-effects from the medication were carefully observed and recorded. They were very rare and were observed both in the d-amphetamine group (6 cases) and in the placebo group (4 cases). In most cases they consisted in uncharacteristic abdominal colic of mild degree, in some cases headache and dizziness. The nature of the side-effects was the same in both groups and stopped gradually whether the therapy was discontinued or not. Likewise, no habit formation was observed in any patient, not even in cases treated continuously for a long time.

### Summary

In a group of 167 inselected cases of obese children, besides food restrictions, every other child was given d-amphetamine sulfate, 2.5 mg three times daily and the others placebo tablets of the same appearance and with the same method of dosage. The weight loss was greater (statistically significant) in the d-amphetamine group than in the control group. D-amphetamine

sulfate is a potent aid in the treatment of obesity also in children, as it is known to be in adults.

### Résumé

Chez un groupe non-sélectionné de 167 enfants obèses, on a, en plus des restrictions alimentaires, donné à un enfant sur deux du sulfate d'amphétamine-d, à raison de 2.5 mg trois fois par jour, et aux autres des comprimés factices de la même apparence et suivant la même méthode de dosage. La déperdition de poids a été plus grande (statistiquement significative) chez le groupe traité à l'amphétamine-d que chez le groupe de contrôle. Le sulfate d'amphétamine-d est un auxiliaire puissant dans le traitement de l'obésité également chez les enfants, comme on sait qu'il l'est chez les adultes.

### Zusammenfassung

In einer Gruppe von 167 nicht ausgewählten Fällen von Fettleibigkeit bei Kindern erhielt jedes zweite Kind neben Kost einschränkung 2,5 mg d-Amphetaminsulphate drei mal täglich und übrigen Blindtabletten mit gleichem Aussehen und mit derselben Dosierung. Die Kinder der Amphetamingruppe zeigten einen statistisch feststellbaren grösseren Gewichtsverlust als die der Kontrollgruppe. D-Amphetaminsulphate, das bekanntlich bei Erwachsenen ein wirksames Mittel ist, ist also auch bei Kindern wirksam.

### Resumen

En un grupo no seleccionado de 167 niños obesos, se ha dado, además de restricciones alimenticias, a cada niño de dos sulfato de anfetamina-d, a razón de 2,5 mgs. tres veces al día, y a los otros comprimidos facticios de la misma apariencia y siguiendo el mismo método de dosis. La disminución de peso ha sido mayor (estáticamente significativa) en el grupo tratado con anfetamina-d que en el grupo de control. El sulfato de anfetamina-d es un poderoso auxiliar para el tratamiento de la obesidad igualmente en los niños que, como ya se sabe, en el caso de los adultos.

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## CASE REPORTS

### Diplomycin Treatment in a Case of Tuberculous Meningitis

by

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Diplomycin, a new antibiotic, and its clinical applicability have been studied in Germany and Denmark during the past two years. The active substance comes from a special diplococcus strain from which it derives its name. Morphologically, this bacterium is an oval or lancet-shaped coccus, growing in pairs or in short chains. Biologically, it mostly resembles *Streptococcus lacticus*. It was isolated by NOSTER (1) in 1945. He accidentally found and unknown gram-positive *Diplococcus* growing in a culture from a patient's sputum. Bacterium-free filtrates of a 1 per cent glucose broth, where this *Diplococcus* had grown, had a bacteriostatic as well as bactericide effect (1, 2, 3, 4). NOSTER considered this effect to be connected with the bacterial secretion products. It seemed to be pronounced both on gram-positive and gram-negative strains, a. o. on tubercle bacilli.

Diplomycin is produced in Germany and Denmark for clinical use. The filtrates differ for local application and for intravenous administration. So far, no preparation has been obtained that can be injected intramuscularly.

The toxicity of diplomycin is very slight. No changes have been observed in the blood, nor has any damage been noted in the kidneys or in the nervous system as, for instance, in streptomycin therapy, although diplomycin was administered daily to patients for several months.

Diplomycin has a conspicuous smell of broth. Immediately after an injection, most of the patients were subjected to a flushing of the face and heart palpitations. They also complained of a marked heat sensation in the body and a headache. However, these symptoms disappeared after a few minutes. The headache may occasionally last for one or two hours. Also a short rise in the temperature, sometimes accompanied by a chill, has been noticed, some hours after the injection. According to the experience collected, one daily injection of diplomycin seems to be sufficient.

Our attention was drawn to this remedy by the statement that diplomycin has an effect on tubercle bacilli. Thus, KLIMANEK (quoted by NOSTER) (5) found diplomycin useful in the treatment of pulmonary

tuberculosis. VIKING (6) treated 3 cases of tuberculosis with this drug; one case of T. b. in the kidneys, another in the bladder and a third with T. b. adenitis with a fistula. The first-mentioned case became free from bacteria in the urine during the diplomycin therapy. The other two cases also recovered rapidly during the diplomycin course. In VIKING's opinion, diplomycin is apparently superior to streptomycin in the treatment of T. b., owing not only to the absence of toxic by-effects, but also to its bactericide as well as bacteriostatic action.

In February, 1950, we decided to try diplomycin treatment in a desolate case of tuberculous meningitis, admitted to the Pediatric Clinic of Kronprinsessan Lovisa's Children's Hospital (K. L. B.).

Hospital Record Number 1247/1949. A boy, aged 7 years. Previous history of no interest. Acutely ill during the first days of November 1949. Examined at a county hospital where the diagnosis of tuberculous meningitis was established. Transferred to K. L. B., on November 14th of the same year, in a bad condition. The diagnosis was confirmed, a. o. with positive guinea-pig test in C. S. F. which also contained approximately 300 leukocytes/mm<sup>3</sup>. A streptomycin treatment was immediately introduced, with a daily dosage of 0.04 Gm of streptomycin intrathecally and 0.15 Gm of dihydrostreptomycin intramuscularly three times daily. This treatment was continued until February 7th, 1950. During this time, sulfonazin and paraaminosalicylic acid (PAS) were given at intervals. In the first weeks the patient showed a gradual improvement, but soon grew worse again, being stuporous or semistuporous all the time. C. S. F. contained, during the first weeks of February, numerous tubercle bacilli and the cell count had increased to about 2000 leukocytes/mm<sup>3</sup>. On February 8th, he manifested a slight left-sided facial paresis, and the pupillae were wide and lacked response to light. On this day (*after nearly three months of unsuccessful streptomycin treatment*) the diplomycin treatment was initiated. During the first three days, he was given 2.5 ml of a so-called A-filtrate intravenously. On the following day 2.5 ml of a C-filtrate was administered. From the fifth day of treatment, he obtained 5 ml of A-filtrate and 2.5 ml of C-filtrate intravenously every day. From February 26th, a daily dose of 5 ml B-filtrate was given, being especially purified for intravenous use. The latter was continued up to March 3rd, whereafter 2.5 ml C-filtrate was given up to April 29th, antihistamin drugs being applied to eliminate the chill and fever in connection with the injections.

Already 9 days after the introduction of the diplomycin treatment, the patient revealed a slight improvement. He was no longer stuporous, and his body temperature, which had earlier been continuously raised, was now constantly normal (Fig. 1). In the following week, he improved remarkably, began to speak, read books, and his memory returned of the time previous to his illness. His neurological status became normal, and

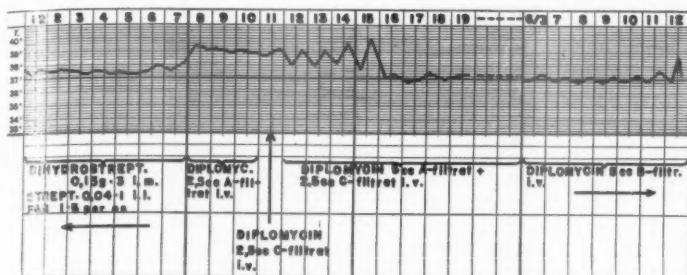


Fig. 1. Temperature chart.

on the last part of April, 1950, the C. S. F. showed a cell count of 12 leukocytes/mm<sup>3</sup>. Repeated guinea-pig tests were negative. His condition is now excellent, he has a good appetite, his body weight is increasing, he can raise himself, stand up and walk without help, and his mental status seems fairly intact.

In 1949, LICHTENSTEIN and MELIN (7) demonstrated that electroencephalography is a valuable method for control of the intracranial tuberculous processes. The different stages of the disease can be registered and relapses traced early by means of serial examinations. All the cases examined showed a fair correlation between the clinical courses and the electro-encephalographic findings.

This case was studied by electro-encephalography immediately after his admission to the hospital, i. e. 13 days after the onset of his disease and before any treatment was given. The registered record was markedly pathologic. Frequent control examinations showed records of the same type every time. Sometimes there was an increase of faster frequencies, but the record was throughout dominated by large slow waves (Fig. 2).

An EEG-examination, 12 days after the diplomycin treatment was begun, showed a record with about the same characteristics as previously, though with a pronounced increase of the faster frequencies. During the following weeks, the faster frequencies gradually accentuated their dominance in the records. EEG:s at the end of March and in April and May of 1950 have been normal with a well established occipital ground frequency of 8-9/sec.

In the present case the electro-encephalographic examinations clearly coincided with the clinical improvement. In the light of earlier experience in this field, these observations confirm the curing of the patient's disease.

Diplomycin, discovered by NOSTER and clinically tested by German and Danish physicians, has here been applied for the first time in the treatment of tuberculous meningitis. A patient, suffering from such a

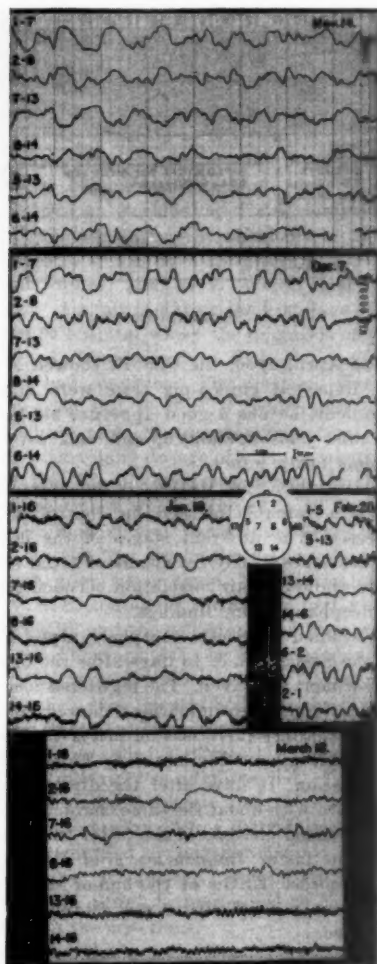


Fig. 2. Electro-encephalograms during the course of the tuberculous meningitis. The figures on the left side of the records refer to the different electrode positions which are marked in a sketch of the head. Technic according to LICHTENSTEIN and MELIN (7).



bacteriologically verified meningitis, had for three months undergone treatment with streptomycin, sulfonazin and paraaminosalicylic acid, though without success. When this treatment was discontinued, his condition was exceedingly bad. C. S. F. contained a large amount of tubercle bacilli. Intravenous diplomycin treatment was introduced, and already after about 9 days a striking clinical improvement was noted. The tubercle bacilli disappeared from the C. S. F., the previously very high cell count went down almost to normal, and the electroencephalogram was normalized. In view of the previous apparent hopelessness of the case and the unsuccessful streptomycin therapy, the diplomycin treatment can hardly be deprived of the credit for this remarkable improvement.

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### Hypoplasia of the Mandible as a Cause of Respiratory Difficulties in the Infant

by

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Chief: Professor C. GYLLENSWÄRD*

Hypoplasia of the mandible — in association with glossoptosis and often with palatoschisis — as a cause of respiratory difficulties in the infant has been described by several authors. As PIERRE ROBIN was the first to study the mechanical effects of ptosis of the tongue (1, 2), the syndrome is often referred to by his name. NISENSEN (3) has recently published a case of receding chin and glossoptosis, and in this connection he has also given a review of 19 similar cases found in the literature. All of these showed deficient development of the lower jaw and glossoptosis. Fifteen had a cleft palate. Troubled breathing and difficulty in swallowing were the dominating clinical symptoms. In 11 cases of these 19, the respiratory difficulties were so severe that they resulted in cyanotic

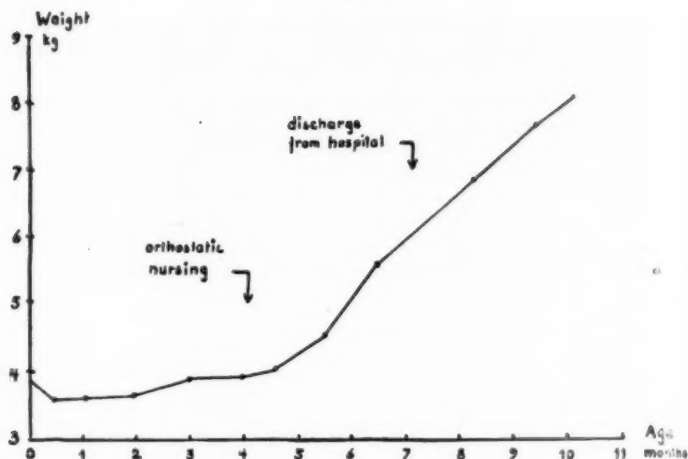


Fig. 1. Case 1. Weight curve.

attacks. According to ROBIN, the respiratory difficulty may even result in retarded physical development, and if the disease is not diagnosed in time there is risk of death from glossoptotic cachexia. It is evident that the difficulty is due to the receding chin and to the mechanical obstacle formed by the tongue, which falls backward and obstructs the passage of the air. The etiology of the deformity is not known. It has been attributed to an arrestment of development, malnutrition, abnormal pressure in the uterus, and so on. Various methods of treatment have been proposed. In general, the authors have counted on the normal growing tendency of the lower jaw, so they have taken steps only to help the infant to get over the first and most difficult period. According to ROBIN, the simplest thing to do so is to put the child in a prone position with a pillow under the upper part of the chest. The tongue then falls forward by its own weight, leaving the pharyngeal passage free. In addition, Robin advises nursing in the same position, with the mouth turned upward like a sucking calf, "orthostatic nursing". Some authors claim to have stimulated the development of the lower jaw through constant pulling with the aid of some headgear (4) or by a special traction apparatus (5); others, referring to successful experiments, recommend a mechanical device on the bottle that forces the infant to push its chin forward in order to suck (6). A brace behind the anguli mandibulae to lift the lower jaw forward (3, 7, 8) has often been tried. In a few cases tracheotomy has even been performed (9). In 1946 DOUGLAS introduced



Fig. 2. Prone position. Age 4 months.

a plastic operative procedure in order to correct the retroposition of the tongue (10). The principle of the operation is a fusion of the tongue to the lower lip. In 5 of DOUGLAS' 6 patients no further symptoms appeared after operation.

#### *Case Reports*

*No. 1.* L. K. B., male, born Jan. 13, 1948. There were no malformations in the family. Delivery was normal and at term. The birth weight was 3 950 g. The lower jaw was very small. The whole of the soft palate and half of the hard palate were cleft. The child could not take the breast and even spoon feeding was difficult. From the beginning a certain respiratory trouble was noticed. The breathing was fast and stertorous. Otherwise the examination was negative.

On the second day the infant was taken from the maternity hospital



Fig. 3. Supine position. Age 4 months.

to the children's hospital. After only two days we were compelled to start tube feeding. On the fifth day pharyngitis set in and his condition changed for the worse. In spite of a sudden fall in temperature after penicillin treatment, the respiratory and swallowing difficulties increased. The breathing became more stertorous and was clearly more laboured. The infant preferred the opisthotonos position. Both awake and asleep he was extremely restless. After two months an increasing tendency to cyanosis was noticed which soon developed into real cyanotic spells. The condition was unquestionably alarming. The anatomic findings in the pharynx could hardly, in our opinion, be considered a sufficient explanation of the child's state. Congenital malformation of the heart was suspected but could not be verified.

When the infant was 4 months old he was in very poor condition. In spite of the usual feeding he had not yet reached his birth weight, and was slack, listless, and feeble. We did not realize until we saw NISENSEN'S



Fig. 4. Prone position. Age 10 months.

(3) paper that the illness might easily be ascribed to the glossoptosis and hypoplastic lower jaw. We decided to try the simplest method of treatment suggested by the literature: the prone position and "orthostatic feeding". The result of this treatment was surprisingly good. The cyanosis disappeared at once. Feeding could be managed easily, even with a bottle. The breathing became calmer and more regular at once, and was but rarely stertorous. Sleep became quiet and undisturbed. The Erythrocyte Sedimentation Rate, which earlier had been constantly 0 (possibly because of hypoxemia with reactive polyglobulia), went up to normal. The remarkable improvement will probably be best shown by the weight curve (Fig. 1).

To get an idea of the state of the pharynx, and especially of the importance of the change in position, we took x-ray photographs of the pharynx in both the prone and the supine positions.<sup>1</sup> The air column in the

<sup>1</sup> My thanks are due to Dr TORE RYDMAN for the x-ray photographs.



Fig. 5. Supine position. Age 10 months.

hypopharynx and in the epipharynx proved more distinctly marked and somewhat broader in the prone position (Fig. 2). In the supine position the tongue fell backward and obstructed the passage of the air (Fig. 3). It has, of course, been difficult to judge, but our point of view was supported by an x-ray examination of normal children of the same age. They showed a broader air column, as broad in the prone as in the supine position.

The infant has developed quickly ever since and since the age of 7 months has been tended in the usual way. No swallowing or respiratory difficulties whatever have been noticed. A new x-ray examination at the age of 10 months showed in both the prone (Fig. 4) and the supine positions (Fig. 5) broad and distinctly marked air columns in the hypopharynx, the same as those of normal infants. The lower jaw has grown, but is still small.

No. 2. A. K. M. M., female, born Feb. 23, 1949. A maternal uncle has a cleft palate. The patient's twin sister (uniovular) has a cleft palate but a nearly normal lower jaw. Delivery was normal and at term. The birth weight was 2 850 g. The lower jaw was small. Breast feeding was not possible, but bottle feeding met with no difficulties. The infant was discharged from the maternity hospital at the usual time. From birth she vomited frequently. The mother failed to notice any respiratory trouble but stated that the girl, unlike her twin sister, snored a lot. Owing to repeated projectile vomitings and slow gaining, she was admitted to the children's hospital on April 13, 1949, at the age of 7 weeks. Her weight was then 2 820 g. Her flesh was flaccid. In a supine position, especially during sleep, her respiration was stertorous and irregular. When she was placed in a prone position her respiration became normal and she seemed to be more comfortable. She ceased vomiting and began to gain weight. After nine days she was discharged. At home she has been kept mainly in the prone position. There were no respiratory difficulties. At the age of 4 months her weight was 4 060 g.

### Summary

Hypoplasia of the mandible in association with glossoptosis and often with palatoschisis is a not altogether unusual disease, often serious and probably not seldom overlooked. Of the 2 cases described here, the first one in particular is interesting. It shows the effect, in this case no doubt life-saving, of a simple and logical therapy: the prone position and "orthostatic feeding".

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## Acute Quinidine Poisoning in a 3 Year Old Child

(With special reference to the electrocardiographic changes)

by

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*Head: O. ELGENMARK, M. D.*

Quinidine, the stereoisomere of quinine, is a general protoplasmic poison and sensibility for it varies considerably. Poisonous symptoms have been observed even after small therapeutic doses, but as a rule the tolerance is quite good up to several grams daily. Quinidine is rapidly absorbed in the alimentary canal. It can be demonstrated in the blood for about 24 hours after peroral administration. In the first 6 hours the greater part of the drug (about 2/3 of the perorally administered dose) will be excreted with the urine.

The action of quinidine on the heart can be summarized as follows: The frequency of beats is diminished without producing irregularity. The excitability of the muscle is reduced by elongation of the refractory period and by diminution of the number of contractions of the auricles and ventricles. Conduction is prolonged through an action on the cardiac muscle and conducting mechanism.

Numerous investigations have established (1) that quinidine produces definite electrocardiographic changes on the human heart; (2) that it is rapidly eliminated from the cardiac structures and (3) that little cumulation of the drug takes place in the heart. The ecg changes consist of a decrease in the amplitude of the positive T waves in all leads, prolongation of the QRS time and impairment of AV conduction and of intraventricular conduction. As cumulation of the drug in the cardiac structures is of no importance, it is the size of the individual dose and not the total period of dosage that determines the magnitude of the ecg effects of quinidine.

According to the observations of Messeloff, based on a series of 10 children with rheumatic heart disease treated with quinidine sulfate, "the principle of dosage and of cumulation governing the clinical use of the drug in children appears to be identical with those reported in adults". He also states that "quinidine may be safely administered to a child in doses proportionally very large for the age and the weight of the subject".

As indication for quinidine treatment in children is very rare, there have not been many opportunities for studying its toxic effects. That is why the following case of an accidental intoxication may be of interest — the dose of quinidine being very large.



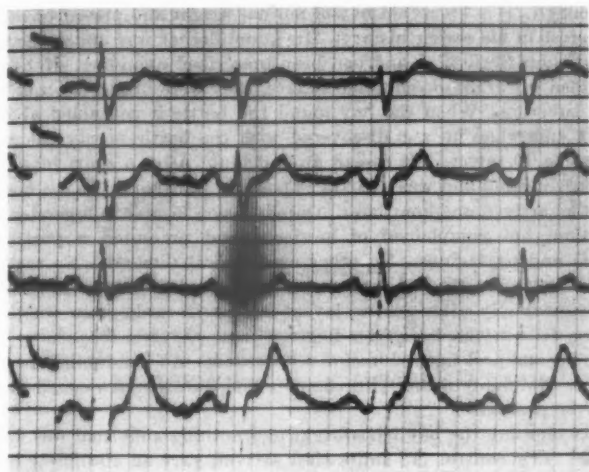


Fig. 1.

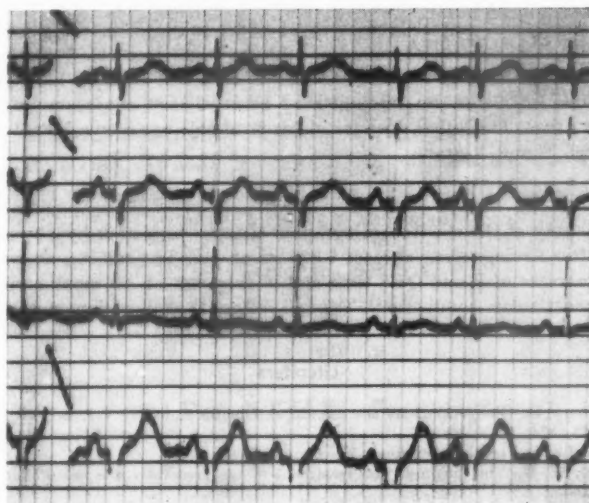


Fig. 2.

Henry L. is a 3 year old boy of normal weight and presented nothing of interest in his earlier history. His grandmother was under treatment for auricular fibrillation and had been prescribed quinidine. Her tablets contained 0.1 gram of quinidine sulfate, they were bright red and had a sugar covering. When the boy found the bottle it contained about 70 tablets and when he was discovered with the bottle empty there were only some 10 tablets left spread around him. After a short interval he started vomiting and was as soon as possible transported to the hospital, where he arrived one hour later. On admission he was in a good general condition, but complained of headache and presented a pronounced vertigo and nystagmus. No other neurological remarks. No rash. No signs of acidosis. He had a moderate bradycardia, pulse rate being 62, and immediately after gastric lavage an electrocardiogram was taken.

Ecg demonstrated (fig. 1): Regular sinus rhythm, frequency 78. P waves big and prolonged, duration 0.12 seconds. AV conduction increased to 0.18. Notching of the QRS complex and duration prolonged to 0.08. T waves positive.

Next morning the boy felt allright and nothing abnormal was demonstrable. Ecg control (18 hours after arrival) gave an absolutely normal result (fig. 2): Frequency now 112. P waves normal, duration 0.06 seconds. AV conduction 0.12 and QRS complex normal, duration 0.05. T waves positive as before.

The urine was collected for 24 hours and measured 700 ml. A sample was sent to the central laboratory of Södersjukhuset in Stockholm for analysis of its content of quinidine and the result was  $165 \pm 5$  mg % of quinidine sulfate. Thus there was an excretion of at least 1.1 gram of quinidine sulfate, corresponding to an absorption of minimum 1.6 gram of the drug. The lethal dose for children of this age is considered to be between 2 and 3 grams.

### Summary

A study of the electrocardiographic changes presented by a 3 year old boy after having taken at least 1.6 gram of quinidine sulfate. Characteristic increase of P and QRS time and impairment of AV conduction and intraventricular conduction. Control after 18 hours demonstrated a normal ecg.

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NORRTULLS SJUKHUS,  
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Vol. XXXIX. Fasc. 4—5

1950

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1950

# ACTA PÆDIATRICA

EDITOR PROFESSOR A. WALLGREN

NORRTULLS SJUKHUS,

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**ADOLF LICHTENSTEIN**

On the 21st of July last, Adolf Lichtenstein, Professor Emeritus of Karolinska Institutet, Stockholm, and Chief Editor of the *Acta Pædiatrica*, died after only a few days' illness. His death

is a severe loss not least to the *Acta*. Lichtenstein had been a member of the Editorial Board of this Review from its very start in 1919. On the death of its founder and first Chief Editor, in 1946, the late professor I. Jundell, Lichtenstein was appointed to succeed him. With much devotion and unwavering energy he took up the task he made up his mind to achieve, that of placing the *Acta Pædiatrica* in the first front rank of European reviews within its special sphere. There is no question but that the four years of his firm, strongly individual and independent, leadership have constituted a period of progress for the *Acta*. Scientifically, its contents have generally kept on a high level. It has improved its standard, and has become more generally read. Lichtenstein's personal contributions added greatly to the value, and current interest, of the review. From its first issue, the *Acta Pædiatrica* has had the privilege of publishing most of Lichtenstein's, and his coworkers', production. The *Acta Pædiatrica* is an international review, its special task being to collect works from the Northern Countries and from Holland. It, thus, serves as a link between the pediatricians of these small countries. During his work as Chief Editor of the *Acta*, Lichtenstein materially contributed to the strengthening of this scientific cooperation. His keen interest in promoting international initiatives manifested itself also in other directions. He was one of the most active pioneers of the *Nordisk Medicin*, the joint organ of the medical societies of the Northern countries. As late as last year, he was a member of the Board of *Nordisk Pædiatrisk Förening* (the Northern Pediatric Society). Lichtenstein participated in the organization and work, of all the Northern pediatric congresses that have so far taken place and was designated for the office of President at the Congress that is to be held in Stockholm in June of next year. By his death, Northern pediatrics have not only lost a very efficient Chief Editor of their scientific publication, the *Acta Pædiatrica*, but also one of the forefront figures of joint pediatric research in these countries.

## On Thrombosis in Children

by

MAIJA MIETTINEN

Thrombosis is a disease which mostly occurs in adult patients and is comparatively rare in infancy.

*Venous thromboses* may occur, for instance, in the mesenteric vessels, giving a clinical picture of intestinal obstruction, or in the portal vein, causing enlargement of the liver and the spleen and formation of ascites. A characteristic clinical picture consisting of splenomegalia, haematemesis and anaemia (KLEIN-SCHMIDT, WALLGREN, NOBEL and WAGNER and HEINIÖ) results from thrombosis in the splenic vein.

However, it is the *obstructions of the dural venous sinuses* that constitute the most important group of venous thromboses. This condition, which has long been known, was first described by MORGAGNI in 1717. The earliest cases were diagnosed in adults but later literature mentions numerous cases of sinus thrombosis in children also (ZISCHINSKY, BYERS and HASS, EBBES, FOLLIS). Thrombosis of dural sinuses has been most frequently described, while occlusion of internal cerebral veins has been less frequent (EHLERS and COURVILLE).

The frequency of thrombosis in the intracranial veins is difficult to estimate, as many cases show no symptoms and it is very rarely that a diagnosis can be made in the lifetime of the patient. The disease is usually not revealed until autopsy. In Baltimore sinus thrombosis was discovered in 1—2 % of post-mortem examinations on children (HOLT).

Thromboses of cerebral veins are usually divided into *primary* and *secondary*, or infectious, types.

In *primary thrombosis* there is no obvious infection, although signs of infection are often revealed at autopsy. On the other hand, these patients suffer often from a serious disturbance of the gastro-intestinal system and acute dehydration, less frequently from chronic malnutrition, which conditions might in themselves promote the development of thrombosis. — The patients also sometimes have severe anaemia. In most cases, however, the aetiology remains quite doubtful. — Cases have been reported in which thrombosis has followed a local trauma or a cerebral operation, or even operations in other parts of the body (EVANS). Sinus punctures have likewise sometimes been suspected (IANCOU) of causing thrombosis, and, above all, sinus injections (SIMPSON). The question has also risen whether infusions of cranial veins are as harmless as has been supposed (HOLT); examples have been cited of sinus thromboses following such infusions (HANSEN). According to EBBS and also BYERS and HASS, sinus thromboses have increased in recent times, but it is impossible to say whether this fact has anything to do with the increased use of injection therapy.

*Secondary thrombosis* always implies the presence of infection. This thrombosis is most commonly connected with mastoiditis caused by otitis and almost equally often with meningitis. Sometimes it is traceable to sepsis or some acute infection, occasionally an infection of the scalp, osteomyelitis of the skull or an infection in the nose or the paranasal sinuses.

When comparing the frequency of primary and secondary thromboses we should mention that in, for instance, BYERS's and HASS's series of 50 cases, 24 were primary and 26 secondary thromboses. Of the former 16 had a severe gastro-intestinal disorder. Of FOLLIS's 78 thromboses, on the other hand, 46 were due to infection, 17 were connected with trauma or a cerebral operation and 15 were primary. Thrombosis of the cerebral sinuses generally occurs in early infancy, if we rule out the thrombosis due to local infection which might arise at any age. In EBBS's and BYERS's and HASS's statistics the majority of the patients suffering from primary thrombosis were under 2 years, most of them under 1. They could not establish any difference in the

proneness of the sexes to the disease, as there were just as many girls as boys.

The *localization* of the thromboses depends on aetiological factors. For example, in connection with otitis and mastoiditis the lateral and sigmoidal sinuses generally become thrombosed, and when the thromboses are connected with meningitis or when they are primary, the disease usually begins in the longitudinal sinus. In lesions of the nasopharynx, orbita and the cerebral basis, the thrombus may extend as far as the sinus cavernosus. The thromboses of the inner cerebral veins, on the other hand, are generally either of the primary or the septic type. The extension of the process may vary greatly. The thrombosis may be limited to a small part of one sinus or spread from its original starting point to several sinuses and cerebral veins.

The occurrence of *changes* in the *cerebral tissue* depends on the localization, extent and duration of the thrombi, and other circumstances. In some cases no drastic changes can be noted, but if the site of the thrombosis is such as to impair cerebral circulation, secondary changes present themselves in the corresponding areas. Among such changes we may mention congestion, cerebral oedema, slight haemorrhages and softened areas. The changes originate in the cortex if the outer venal system has become obstructed and in the basal ganglia in case of damage to the inner veins.

The *clinical picture* varies considerably in different types of thrombosis. In *secondary* types the symptoms depend upon the primary disease. Thus in thrombosis of the lateral and sigmoidal sinus caused by otitis and mastoiditis we have a complex of symptoms which is well known and is considered characteristic of this disease, so that there is no reason to deal with it in more detail here. The symptoms of *primary* thrombosis as well as of thromboses with an unclear aetiology are so varied that no consistent clinical picture is produced. Yet these cases may have quite a number of common features. A great number of the patients have a severe gastro-intestinal disturbance before the appearance of the thrombotic symptoms, vomiting, diarrhoea, or dehydrational, more seldom chronic, marasmus. Some of the

children have previously been quite healthy, and the disease begins suddenly. The child becomes tired and sleepy and at the same time very restless. High temperature occurs in almost all cases, but it varies greatly. The blood cultures are usually negative, in contrast to those taken in secondary thromboses, which generally give a positive result.

The most common of the *local cerebral symptoms* are spasms, clonic convulsions and local paralysis. To begin with the convulsions may be of the Jackson type, in a definite part of the body, but in many cases they become general. General muscular rigidity and opisthotonus, with the head bent backwards, are important symptoms, especially characteristic of thrombosis of the direct sinus and the Galenic veins. In some cases there are no symptoms of intracranial pressure, or they occur only very late. Disturbance of consciousness is very common among thrombotic patients. Often the child loses consciousness almost at the onset of the disease, sometimes periods of consciousness and unconsciousness alternate, and occasionally the child is active and conscious for a long time and does not fall into a coma until shortly before death. In other cases cyanosis of the face, oedema of the scalp and swelling of the cranial veins have been noted. In thrombosis of the sinus cavernosus exophthalmus may occur on the diseased side, as may oedema of the lids and chemosis, and dilatation of the retinal vessels. If the thrombosis of the lateral sinus continues into the jugular vein, it may be felt as a hard cord on the neck. A lumbar puncture may sometimes provide important diagnostic hints. The pressure may be normal or above normal, cells may be lacking or they may be somewhat increased in number. What is most important is to establish the presence of erythrocytes or of xanthochromic liquor. EBBS stresses the importance of an increase in chlorides in the spinal fluid. Usually no bacteria are found. The Queckenstedt sign is significant in establishing unilateral thrombosis of the lateral sinus.

In *differential diagnosis* meningitis, cerebral abscess, cerebral tumours, cerebral haemorrhage and encephalitis must above all be distinguished. Usually the three first may easily be ruled out,

but haemorrhage and encephalitis may produce quite similar symptoms. It is often particularly difficult to distinguish encephalitis from primary thrombosis.

The *prognosis* of thrombosis in cerebral sinuses is generally bad. The course of the disease is conditioned by the localization and extent of the thrombosis and in secondary forms by the primary disease. Mild and symptomless cases may be cured, but in thrombosis with symptoms mortality is very high. Especially thrombosis of the internal sinuses and inner cerebral veins leads to death almost without exception. The death occurs either within a few days or weeks from the beginning of the cerebral symptoms.

*Treatment.* — Surgical treatment gives good results in many types of secondary thrombosis, e.g. occlusion of the lateral sinus, but in primary forms and also in other more extensive thromboses all treatment, even treatment with heparin, is usually ineffective.

Since primary sinus thromboses are rather rare in children and as diagnosing them is difficult, I shall present the following case treated at the Pediatric Clinic of Turku University.

A boy aged 1 year and 10 months was admitted to the hospital Sept. 20, 1948.

There was nothing noteworthy in the family. The child was born at term and delivery was normal. He was active from birth and according to his mother developed normally both physically and mentally. No symptoms indicating birth trauma were noted. He learned to walk at 11 months and even spoke a few words. Though healthy otherwise, from 4 months on he had several mild attacks of convulsions in which he lost consciousness for a short time. There was no rise in temperature during the convulsions and after them he seemed quite well. The last convulsions were in May, 1948, and as before recovery seemed complete. On Sept. 17, 1948, he suddenly developed a high temperature and had a slight fit of convulsions. Thereafter he was continuously unconscious and had occasional convulsions. There was no pain in the ears, no diarrhoea nor vomiting.

*Status praesens* Sept. 20, 1948. — The patients' general condition was poor. He was pale and hollow-eyed. Temperature: 39.5° C. He was slightly built, but fairly well nourished. The subcutis was very much reduced. Turgor was very poor. He was completely unconscious, did not respond to pinching, the corneal reflexes were dead and he was unable to swallow. He was limp but during the examination easily fell

into a state of convulsions during which especially the upper limbs became rigid, the wrists and fingers curled round and there were slight spasms in the hands. There was no rigidity of the neck. The Kernig test was negative. The reflexes were symmetrical and lively. The eye fundi were normal, the ears healthy. Lungs, heart, digestive organs and genitals showed nothing special. There was neither albumin nor sugar in the urine; Gerhard and Lange tests were positive. Tuberculin and WR tests were negative. The sedimentation rate was 14 mm/1 hr. The blood count showed slight leukocytosis, which increased in the course of the disease. Lumbar puncture: liquor clear, colourless, pressure normal. Pandy, Nonne and WR negative, no cells and no bacteria. In repeated punctures the liquor remained normal at any rate until Sept. 25, 1948, after which no more lumbar punctures could be made because of the patient's posture.

*Decursus morbi.* — At hospital the patient remained unconscious all the time, although the dehydration and the acidosis could soon be cured. Temperatures ranging between 38—39.6° C persisted almost to the end, practically without interruption. For a week there were sometimes Jackson type, sometimes common convulsions, which gradually became almost continuous. After this the rigidity increased, while wrists, fingers and toes were in a maximal flexion and the limbs could not be moved even passively. At the same time the head began to bend backwards and opisthotonus developed, becoming more and more intense until 19 days after the onset of the disease the heels touched the back of the skull and finally the back of the skull touched the gluteal region (Fig. 1 and 2). The patient was altogether so spastic that it was impossible to change his position at all. The whole time no signs of papillary oedema were noticeable in the eye fundi. With the symptoms remaining unchanged and the general condition growing worse the patient died Oct. 14, 1948, 28 days after the onset of the disease.

At the *autopsy*, which was made on the same day, extensive thrombosing of the cerebral venous sinuses was noted. The sinus sagittalis superior as well as the meningeal veins running into it were completely filled with a thrombic mass. The sinus sagittalis inferior, the sinus rectus, the sinus transversus bilaterally, the left sinus sigmoideus and the left v. jugularis interna and communis almost as far as the v. subclavia sinistra were also thrombosed. The vessels of the cerebral basis were normal. The walls of the blood vessels mentioned were smooth and there were no macroscopic changes. The leptomeninges were somewhat turbid and thickened in places. The cerebral consistency was relatively soft and the gyri remarkably flattened. The cut surface of the brain was moist; the grey matter in the cortex and in the basal ganglia seemed somewhat swollen. No haemorrhages nor softened areas could be seen in the cut surfaces. The ventricles contained clear liquor. The ependyma



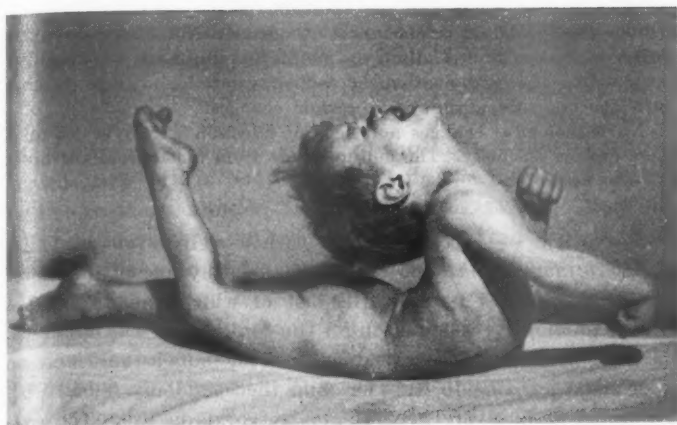


Fig. 1.



Fig. 2.

was smooth everywhere and the choroidal plexus normal. The pons, medulla oblongata and cerebellum were normal. No changes were noticeable in the spinal cord. Both the middle and inner ears were healthy. In the microscopic examination the meninges were found to be oedematous. The brain tissue showed no certain changes.

No pathological changes nor signs of infection were revealed anywhere else in the body. The culture made from blood from the heart was also negative.

*Discussion.* — We have to do with a well developed child, 1 year 10 months old, who earlier was healthy except for fits of convulsions from 4 months, the last of which had occurred 4 months previously. The reason for the convulsions was unknown, but there might have been trauma at birth, though there were no other signs pointing to it. The child then suddenly fell ill with symptoms of a severe general and cerebral disease. The outstanding features of the clinical picture were a high temperature, acute dehydration and acidosis, continuous unconsciousness, convulsions, with rigidity developing later, and very severe opisthotonus. As the clinical picture was exceptional and very peculiar, the diagnosis remained unclear, although the case was first considered one of encephalitis. Sinus thrombosis, which had spread widely, was established by the post mortem examination.

Yet the aetiology of the thrombosis remained doubtful, as no infectious focus was found in the autopsy. No skull trauma could be discovered, and the patient had not been given infusions into the cranial veins and the sinus. The case may thus be classified as belonging to the primary thrombosis group. Regarding the causes likely to promote thrombosis, we note two facts in this case. First the child's convulsions, which — in common with other physical exertion — are known to shorten the blood coagulation time (VUORI and associates). Secondly the severe acute dehydration, which may be accounted for by the fact that the child was unconscious at home for three days and was not given any liquid. Possibly these two facts might have provided the conditions favourable for an onset of the disease, although they do not entirely explain it.

*Obstructions in the arterial circulation* — due to embolism or thrombosis — are still rarer in childhood than venous thrombosis. Coronary thrombosis, which is such a common disease in adults, is very infrequent in children, though it has actually sometimes been found even in infants (RAMSAY and CRUMRINE). Obstructions of smaller arteries giving rise to limited gangrenes in different parts of the body or infarcts in the internal organs are more frequent. DOHAN, HELLER and ALVARI and GROSS have published extensive surveys of the literature dealing with gangrenes in the extremities of newborn babies, while v. KHAUTZ and MARTIN and SHORE have surveyed the literature on gangrenes in older children. In the literature I have found a total of 48 cases of limb gangrenes in the newborn. The gangrene was in the lower limbs in 31 cases, in 10 in the upper limbs, in both the upper and lower limbs in 3 cases and in other parts of the body in 4 cases. In older children 45 cases of limb gangrene were noted, usually in the lower limbs. In some of the gangrenous cases no thrombotic obstruction occurred in the arteries, but the gangrene was sometimes supposed to have been caused by angiospasm resembling Raynaud's disease, sometimes by a kind of agglutination of the intima (HELLER and ALVARI), or by a protracted compression during delivery.

*Obstructions in the aorta* and its largest branches are very rare in children, on the other hand. ROTHSTEIN collected a series of 12 such cases from the literature, BECKER and GIRGENSOHN reported on 3, GROSS also on 3 and LEOPOLD and GOEBEL on 1 case each. Thus the number of published cases of complete aortal thrombosis in children under 15 years is 20. Of these 8 were from birth to 3 weeks old and 12 under one year. LEOPOLD, LÜTTICH, HEDINGER, MOSCHCOWITZ, WHEELER and ROTHSTEIN each describe 1 case of aortal thrombosis in newborn infants and GROSS 2 cases.

There are three possible origins of an obstruction of the aorta, namely embolism and associated thrombosis, the extension of thrombi backwards from the other arteries and the formation of local thrombi.

*Embolism* presupposes the formation of thrombi in the thoracic part of the aorta or the left half of the heart, and in childhood this generally occurs only in cases of endocarditis and chronic myocarditis, more rarely in cyanotic types of congenital heart diseases. GROSS also stresses the importance of an open or just obliterating ductus arteriosus as a point of formation of thrombi and a point from which emboli may start. In newborn infants even an embolus originating in the veins, e.g. v. umbilicalis, might find its way into the aorta through an open foramen ovale.

In children one seldom meets *thrombi extending backwards* from the arteries of the lower extremities, as they seldom suffer from such severe vascular diseases as arteriosclerosis and thrombo-angitis obliterans. In the newborn, on the other hand, an obstruction in the abdominal aorta may be connected with the thrombosing of the umbilical arteries. Thrombi may form in them after birth, organize themselves, and towards the end of the first week become occluded up to the end. The thrombosing generally does not extend beyond the section of the artery which is no longer used, but in some cases it may spread against the blood stream as far as the a. hypogastrica, a. iliaca, or even the lower part of the aorta (GROSS).

A *thrombus forming locally* in the aorta may sometimes be due to local injury to the wall, possibly caused by trauma or infection, as in mesoarteritis luetica. On the other hand, general injury done to blood vessels by infectious diseases such as sepsis, diphtheria and typhoid fever may account for the formation of thrombi in the arteries.

In the series published it has generally not been specified exactly whether one had to do in each case with embolism or thrombosis. The obstruction of the aorta was attributed to umbilical sepsis in 3 cases, to the formation of a thrombus in a patent or just-obliterating ductus arteriosus in 3 cases, in 3 to severe diphtheria, in 1 to an undefined infectious disease, in 1 to inflammation of the aortic wall originating in the intestine, and in 8 cases no cause could be given.

Thrombosis of the abdominal aorta generally gives a charac-

teristic *clinical picture*. The symptoms usually set in suddenly with a sharp pain in the lower extremities, less frequently in the abdomen or in the back. Numbness, disturbance of sensibility and a feeling of coldness occur in the lower limbs within a few hours. Partial or total paraplegia may also develop. The limbs become cyanotic and later gangrenes form, the extent depending on the completeness of the aortic obstruction and possible collateral circulation. Pulsation of limb arteries ceases in both feet at once or first in one and then in the other. Before long there is a rise in temperature and bouts of vomiting and the general condition declines rapidly. Should the thrombosis extend to other arteries, especially to renal and mesenteric vessels, symptoms of their obstruction predominate. If embolism is the original cause of the aortic obstruction, typical embolic symptoms may also occur in other organs. In most cases death follows in a few days but sometimes the disease may last for several weeks or even months after the onset of the circulatory disturbance. In the 20 cases recorded in the literature the shortest time between the onset of the symptoms of occlusion and death was 18 hours, the longest several months. Gangrene occurred in the lower limbs in 15 cases, while in 5 cases there was circulatory disturbance without any gangrene.

All the children who were affected died. Total occlusion of the abdominal aorta was noted in all at autopsy, the thrombus often extending a longer or shorter way into the a. iliaca. Thrombosis of the renal arteries was also noted in 4 cases, infarcts in the kidneys 8 times, and infarcts in the brain, lungs and spleen in 1 or 2 cases. Further, a thrombus was encountered 3 times in the ductus Botalli, intracardial thrombi occurred once and endocarditic changes in the heart valves twice.

As can be seen from the foregoing, the *prognosis* for aortal thrombosis is very bad. ROTHSTEIN (1935) collected a series of 124 cases in all in which only 12 were children and 113, i.e. 91 %, died. In the 20 cases mentioned all the children died.

Either conservative or operative *treatment* may be considered. In many cases the patient's condition is so poor because of a primary disease or the disease may have lasted so long that ope-

ration is out of the question and therefore only conservative treatment is possible. Others (ROTHSTEIN and associates) emphasize the importance of performing embolectomy as soon as possible. Successful operations have been made on adults, but among children I know of only 1 operative case, and then the patient did not recover.

Because of the rarity of aortal thrombosis in children I shall describe the following additional case treated at the Pediatric Clinic of Turku University.

Boy, aged 3 days, admitted Feb. 15, 1949.

There was nothing noteworthy in the family. The mother was 19 years of age and had always been healthy. Her pregnancy was normal. WR was negative. The delivery, her first, occurred at full term, took 52 hours in all and was difficult, but the child was born spontaneously. Birth weight was 5 100 g. The child was cyanotic at birth but cried at once and was active otherwise. Nothing out of the ordinary was noted in the umbilical cord. For 3 days the child was relatively well barring slight cyanosis, quiet and with a normal temperature. On the fourth day he suddenly became restless, began to shiver, had slight convulsions, and developed a temperature up to 40.2° C. His cyanosis increased.

*Status praesens* Feb. 15, 1949. — General condition: poor. He was restless, whimpered all the time, and had severe cyanosis all over. He was of strong build and well nourished. Length 53 cm, weight 4 500 g. Good turgor. No skin eruption. The skin was of even colour everywhere. Temperature 40.0° C. The umbilical stump was neat and there were no signs of inflammation. He reacted to pinching. There was shivering resembling tremor in the hands and his limbs were slightly spastic. Reflexes were ordinary. There was no rigidity of the neck. The Kernig and Brudzinski signs were negative. Fontanelle tension was ordinary. Breathing was rapid, but there was nothing special in the lungs. The heart was of ordinary size; the heart sounds were clear, with no murmur. Nothing special was noted in the digestive organs and genitals. Lumbar puncture: pressure ordinary, liquor reddish, abundance of fresh erythrocytes, 25 leukocytes, no bacteria. Blood count: haemoglobin content 137 %, erythrocytes 5.98 mill., colour index 1.13, leukocytes 10 600.

*Decursus morbi.* — On the following days there was little change in the patient's condition. He was given penicillin but his temperature still varied between 40.3—37.5° C. He was slightly cyanotic all the time, ate very little, his weight fell and slight dehydration set in. There were convulsions on 3 days, after which he became quieter. The umbilical stump detached itself at the usual time and the navel did not seem inflamed. On the night of Feb. 23, 8 days after admission, the child's

condition suddenly grew worse. The cyanosis increased everywhere, but the lower extremities, particularly, became bluish with lighter and darker patches. During the night the feet turned cold and still bluer and the child died on the following morning aged 12 days.

At *autopsy* a dark, solid thrombus which was firmly attached to the walls was found at the lower part of the aorta, completely closing its lumen. The thrombus began at the point of the first lumbar vertebra, continued downwards to the point where the aorta branched and there to the right into the a. iliaca communis, a. hypogastrica and a. umbilicalis, extending as far as the navel. On the left the thrombus continued 4 cm downwards from the point of division of the aorta into the a. iliaca communis. The thrombus in the aorta covered the point of origin of the a. mesenterica inferior but there was no thrombus in this artery itself. The other arteries starting higher up and the femoral arteries were free. The v. umbilicalis was free as far as the liver with the exception of a small coagulation along the wall quite close to the navel, in which no thrombus nor pus formation was found. No changes were seen by the naked eye in the navel and the umbilical vessels. Unfortunately no specimen was taken from the umbilical vessels for microscopic study and no blood culture was made. The brain, kidneys, spleen and intestines showed nothing pathological. Stasis and oedema were noted in the lungs, and stasis and fatty infiltration in the liver. The endocardium, valves and myocardium looked quite normal. The foramen ovale and ductus Botalli were open.

*Discussion.* — The patient was a very large 3 day old infant born spontaneously but after long and difficult labour. After having been fairly well on the first days the child suddenly developed a high temperature on the fourth day, had slight convulsions and became cyanotic. At examination no definite cause could be established for the high fever and the poor general condition and no symptoms of inflammation were found in the navel. At 12 days of age he suddenly became worse, the lower limbs became cold and blue-mottled, and he died about 16 hours after the onset of the circulatory disturbance. Total thrombosis of the abdominal aorta was revealed at autopsy, continuing on the right in the corresponding arteries as far as the navel. There were no macroscopic changes in the v. umbilicalis and the navel and nothing pathological in the other arteries or in the heart. An open foramen ovale and ductus Botalli are normal findings at this age.

It cannot be said with certainty whether the aortic occlusion was due to embolism or to thrombosis, but thrombosis seems the more likely, since no starting point could be established for the emboli and no infarcts caused by emboli could be found in the other organs.

Regarding the aetiology of the thrombosis it may be noted that the aortic thrombus continued without interruption along the umbilical artery as far as the navel. Thus the idea suggested is that the thrombosing of the aorta may be due to a retrograde development of the thrombosis in the umbilical artery. This possibility is also indicated by GROSS. What, on the other hand, can have caused a thrombic development of this kind farther back than normal? MOSCHCOWITZ, WHEELER and ROTHSTEIN noted one case each of aortic thrombosis due to umbilical sepsis. In the case just described the septic temperature and poor general condition were in agreement with the clinical picture of umbilical sepsis, though no inflammatory changes were noted macroscopically in the navel and the umbilical vessels. Yet many investigators (RUNGE, WERTHEMANN, FINKELSTEIN, HUNT, HOLT, CRAMER, WACHTER) found that clinical symptoms and changes in the umbilical vessels may be so slight in umbilical sepsis that the presence of arteritis or periarteritis, more rarely phlebitis, can be revealed only by microscopic study. As no microscopic sample was taken in this case, the lack of macroscopic changes does not rule out the possibility of umbilical sepsis, so that it is not improbable that an infection starting from the navel may have given rise to the inflammation of the umbilical vessels and thus led to extensive thrombosis.

Asphyxia due to the long and difficult labour, which, as is well known, shortens the coagulation time of blood, and the relative polycythaemia of the child are additional factors conducive to the formation of the thrombi.

### Summary

A short description is given of various venous and arterial thromboses occurring in children. The frequency of sinus thromboses and occlusion of the abdominal aorta, their aetiology and the clinical



pictures are discussed and the literature on these conditions is surveyed. A report follows on a case of sinus thrombosis of the primary type in a 1 year and 10 months old infant and also on a case of total thrombosis of the abdominal aorta in a newborn infant, the aetiology of which was suspected to be umbilical sepsis, though this could not be proved.

### Résumé

On fait une brève description de différents thrombus veineux et artériels qui se sont produits chez des enfants. La fréquence de thrombus de sinus et d'occlusion de l'aorte abdominale, leur étiologie et leurs images cliniques sont discutées et on fait une étude des ouvrages publiés sur ces états. On fait ensuite un rapport d'un cas de thrombus de sinus de type primaire chez un enfant d'un an et 10 mois et aussi d'un cas de thrombus total de l'aorte abdominale chez un enfant nouveau-né; dans ce dernier cas, on a supposé que la cause était une sepsis ombilicale, ce qui, cependant, n'a pas pu être prouvé.

### Zusammenfassung

Verfasser beschreibt kurz verschiedene venöse und arterielle Thrombosen bei Kindern und diskutiert näher die Frequenz, die Ätiologie und das klinische Bild der Sinusthrombose und der Occlusion der Aorta abdominalis. Ein Fall von primärer Sinusthrombose bei einem 1 Jahr 10 Monate alten Kind sowie ein Fall von totaler Thrombose der Aorta abdominalis bei einem Neugeborenen (umbilicale Sepsis?) werden beschrieben.

### Resumen

Se da una breve descripción de diferentes trombosis venosas y arteriales producidas en niños. Se discute la frecuencia de trombosis de seno y de oclusión de la aorta abdominal, su etiología y sus imágenes clínicas, y se hace un estudio de las obras publicadas sobre tales estados. Después se hace una relación de un caso de trombosis de seno de tipo primario en un niño de un año y diez meses y también de un caso de trombosis total de la aorta

abdominal en un niño recién nacido; en este último caso se supone que la causa fué una sepsis umbilical, lo que, sin embargo, no ha podido probarse.

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI  
(HEAD: PROF. A. YLPPÖ) AND THE WOMEN'S CLINIC (HEAD: PROF.  
M. RAURAMO).

## **Investigations into the Histamine Content of Umbilical Blood**

by

**OSSI PETTAY**

Asphyxia as the cause of pathological states in the newborn is arousing an ever increasing interest, and the state of the premature child, especially, is often considered to resemble shock (MILLER, CLIFFORD, ÅKERRÉN). The conspicuous similarity between the premature state and shock is emphasized in particular by ÅKERRÉN. The most important characteristics are an increase in capillary permeability and congestion in the visceral organs, principally the liver.

Some German authors, on the other hand, have observed that the histamine percentage in cats' blood has increased as much as 400 times on the animals' being kept in under-pressure for 10—15 minutes, and that in man the percentage of plasma-histamins and the effectivity of ventilation through the lungs are inversely proportional: in other words, lack of oxygen brings about an increase in plasma histamine (EICHLER, BARFUSS).

Thirdly, physical constraint and rupture of the tissues are also known to contribute to the rise in plasma histamine.

Histamine shock and the state of the new-born are similar in many respects. In connection with delivery a child suffers from lack of oxygen and frequently rupture of the tissues occurs. The child is subjected to great physical exertion at birth. Owing to these facts I decided to examine the percentage of histamine in the umbilical blood.

In human blood, histamine is found mainly in the white blood cells, probably as physiologically inactive (EMMELIN, KATZ,

UNGAR, PARROT, ANREP, BEST). According to Code 70—100 % of the blood histamine is contained in the granulocytes. All histamine in the plasma is generally considered to be in a physiologically active state. In *in vitro* tests, for instance, bacterial toxins and allergens have been found to liberate histamine from white cells into plasma (KATZ, ROSE, FELDBERG).

On study of the total percentage of histamine in hen embryos the histamine was found to increase fairly evenly during the development of the embryo, except just before birth when its production is accelerated (MISRAHY). The percentage of histamine in the lungs of a guinea pig was examined and found to be extremely low in the embryonic stage but to increase during birth several hundredfold (THRETHEWIC).

The histaminolytic power of the umbilical blood is almost similar to that of the blood of adults (SWANBERG). During the last months of pregnancy the histaminolytic power of the maternal blood may be as much as 1 000 times greater (SWEDIN, AHLMARK). Furthermore, the maternal part of the placenta contains more histaminase than any other tissue. In the amniotic fluid there is an abundance of it as well (SWANBERG).

I have found no reports on the percentage of histamine in the umbilical blood in the available literature.

#### Method

I have used a method described by Ahlmark. A quantity of 6—8 ml 10 % trichloroacetic acid is added to 3—4 ml plasma and the mixture is allowed to stand at least one and one half hours. It is then filtered and the precipitate washed four times with 3 ml 10 % trichloroacetic acid, after which it is mixed with 6—8 ml 10 % hydrochloric acid. The mixture is boiled for one and one half hours and then evaporated to dryness. Most of the hydrochloric acid is removed through distillation in a boiling water bath with four portions of 10 ml alcohol. The residue is mixed with 3—4 ml water and a sufficient quantity of Tyrodes solution so that the histamine content in the final test amounts to about 0.3/ml. NaOH is added until the reaction becomes neutral to lit-

mus. The contracting effect of this fluid on the small intestine of the guinea pig in Tyrodes solution of 37 degrees (C) is compared with the effect of known histamine solutions.

Amniotic fluid is rich in histaminase and in taking umbilical blood it is very difficult to avoid getting amniotic fluid with it. In addition to the citrate I added 3 drops of 12 % sodium cyanide, which inactivates the histaminase, to the flask in which the blood is taken. The samples of blood were taken immediately after birth from the placental part of the vena umbilicalis, centrifuged and precipitated with trichloroacetic acid at the latest within eight hours. In the meanwhile the samples were kept in room temperature.

As a rule I used considerably larger amounts of plasma than in the above mentioned method, in order to obtain a suitable histamine concentration.

The blood bank of the Finnish Red Cross kindly supplied me with citrate blood for comparative purposes. I added cyanide to these samples as well and endeavoured to analyze them in the same way as far as possible.

### Results

The percentage of histamine in the plasma of umbilical blood taken in connection with 25 normal births varied from 0.06 to 0.2  $\gamma$ /ml, and in 10 healthy adults from 0.02 to 0.08  $\gamma$ /ml (Fig. 1). The results thus show that the plasma of umbilical blood contains about two—three times more histamine than that of adults.

The fact that more histamine is found in the plasma of the newborn than in that of adults gives rise to speculation concerning its source. Considering the great quantity of histaminase in the blood and placenta of pregnant women, it is evident that the histamine in the plasma of umbilical blood is produced in the foetus itself. Whether the histamine is active in the embryonic stage or liberated during delivery is unknown. The latter alternative seems the more credible.

Immediately after birth the blood of a child, especially that of a premature, contains much organic acid owing to this it is

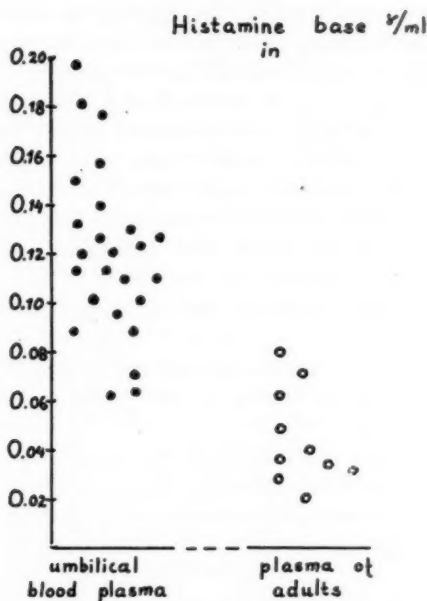


Fig. 1.

evidently more acid than it becomes later (RÄIHÄ, WILSON and associates). This may liberate histamine into the plasma. In order to find out whether Ph affects the histamine percentage in white cells I separated them from adult blood by centrifugation and put them into physiological saline solution the Ph of which was about 6.5 over a period of two hours. No histamine was liberated, however.

Another possibility is that lack of oxygen causes liberation of histamine. Following this train of thought I introduced nitrogen into adult blood, whereupon the percentage of oxygen decreased almost to zero. Owing to this procedure the percentage of histamine in the plasma increased about seven times (Table).

If lack of oxygen liberates histamine for plasma causing physiological activity, it is conceivable that histamine plays an im-

### Histamine Content of Adult Plasma Before and After Introduction of Nitrogen.

Before	After
0.032 $\gamma$ /ml	0.242 $\gamma$ /ml
0.046 $\gamma$ /ml	0.310 $\gamma$ /ml
0.036 $\gamma$ /ml	0.252 $\gamma$ /ml

portant rôle in the mechanism of death from suffocation. The macroscopic-pathologic-anatomic picture of suffocation bears a considerable resemblance to that of a histamine shock. In order to investigate the part played by histamine in suffocation I injected test animals (rats, which are fairly resistant to histamine, and guinea pigs, which are sensitive to histamine) intraperitoneally with large doses of antistine and killed the animals by putting them into nitrogenous atmosphere. I compared the period of survival of the animals given antistine with that of the control animals and weighed the different visceral organs after death in order to find out if there was any difference in the quantity of oedema produced in them. All animals behaved in the same way, however, and the weights of the visceral organs revealed no differences.

Some Swiss scientists (BAUR, STAUB) have found that 15—20 minutes after an injection of adrenalin into man there is a distinct rise in the percentage of histamine in the plasma. It seems probable that during birth a child secretes all adrenalin at disposal, and this may perhaps account for the high histamine value in the plasma. Dr. Pekkarinen, of the Institute of Physiological Chemistry of this university, was kind enough to perform five estimates of the adrenalin in umbilical blood but was not able to find adrenalin in any case. The lowest sensitivity border of the method used by him was about 0.5—1.0  $\mu\text{g}$  %.

### Discussion

The fact that during birth the lungs are the foetal tissue richest in histamine and that on the other hand the amniotic fluid contains large amounts of histaminase is of special interest.

An asphyctic child, at any rate, is known to inhale amniotic fluid into its lungs. If asphyxia is the factor which increases the percentage of histamine in the plasma, these respiratory movements might be a safety valve through which the surplus histamine is removed.

I have calculated that if the histaminase of the amniotic fluid and the histamine of the plasma come to react with one another, in 20 minutes about 25 ml of amniotic fluid will dissolve all the histamine circulating in the plasma of the child.

The great amount of histamine in the umbilical plasma could, at least in part, explain many physiological peculiarities of the newborn baby. WEGELIUS has proved that a haemoconcentration takes place during the first hours after birth. The power of histamine to increase capillary permeability may contribute to this process.

The stomach of the newborn is known to secrete more acid during the first day of life than for a long time afterwards (HUNT-KANGAS, MILLER). This may also be due to the effect of histamine.

In adults KARVONEN *and associates* found that under-pressure causes a decrease in the secretion of the stomach. They consider this due to the fact that the energy required for production of HCl is not available in under-pressure to the same extent as under normal conditions. The disagreement in these results and the theory that lack of oxygen in a newborn increases by means of histamine the secretion of HCl may be explained by the fact that the newborn infant is able to produce energy out of carbohydrates without consuming oxygen (HIMWICH *and associates*). Other similarities between the state of the newborn and that under the influence of histamine are the congestion of the visceral organs, especially the liver and the spleen, and the small effusions on the serous membranes.

I consider the idea of a possible effect exerted by histamine on the physiological activities and the appearance of pathological states in the newborn so interesting that it justifies the publication of the results obtained thus far.



### Summary

The author has determined the histamine percentage of 25 umbilical blood plasmas. Ten normal adult plasmas served as control. On an average the histamine content of the umbilical plasmas was found to be two—three times higher than that of the normal plasmas. This difference is supposed to be due to lack of oxygen during birth.

### Résumé

L'auteur a déterminé le pourcentage d'histamine de 25 plasmas de sang ombilical. Les plasmas de 10 adultes normaux ont servi de contrôle. On a constaté qu'en moyenne le contenu d'histamine des plasmas ombilicaux était deux à trois fois plus élevé que celui des plasmas normaux. On suppose que la différence est due au manque d'oxygène pendant la naissance.

### Zusammenfassung

Bericht über Histamingehaltbestimmungen des Nabelschnurblutplasmas in 25 Fällen. Der Histamingehalt des Nabelschnurblutplasmas (25 Fälle) wurde mit den Werten von Plasmahistamin bei Erwachsenen (10 Fälle) verglichen und durchschnittlich 2—3 mal höher gefunden. Die Ursache ist wahrscheinlich ein Sauerstoffmangel während der Geburt.

### Resumen

El autor ha determinado el tanto por ciento de histamina de 25 plasmas de sangre umbilical. Los plasmas de 10 adultos normales han servido de control. Se ha comprobado que el contenido medio de histamina de los plasmas umbilicales era dos o tres veces mayor que el de los plasmas normales. Se supone que la diferencia se debe a falta de oxígeno durante el nacimiento.

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## On Interstitial Plasma Cell Pneumonia in Infants<sup>1</sup>

by

HARALD GORMSEN

So-called interstitial plasma cell pneumonia, which appears not to have been observed previously in Denmark, is a well-defined nosologic entity with clinical and pathologico-anatomical characteristics which appears almost exclusively in premature infants in the second to third month of life and is characterized pathologico-anatomically by a massive interstitial inflammatory infiltration made up preponderantly of plasma cells.

As the number of surviving prematures may be assumed to be increasing because of the systematized care of these children, it is undoubtedly to be expected that more cases of this disease will be encountered in future. For this reason — and also because the highly characteristic pathologico-anatomical findings in cases of this kind give rise to some pathogenetic considerations bearing on the physiologic aspects of prematures and their treatment — a report will be given here of 2 recent cases of prematures, aged 12 and 14 weeks, respectively, including the autopsy findings and what is known so far about this disease, which still is rare, at any rate in this country.

### Case Records

**Case 1.** The child, a boy, was born about two months before term of a healthy primipara, married, aged 25. Delivery was spontaneous. The birth weight was only 1 450 g, the length 39 cm. During the first ten days after birth the child was taken care of in the Lying-In Department B (1848/47) of the Rigshospital, from which he was transferred to

<sup>1</sup> Read at the meetings of the Danish Pathologist Association on April 21, 1948 and of the Danish Society of Pediatricians on March 9, 1949.

the Municipal Children's Hospital, Martinsvej, Copenhagen<sup>1</sup>, where he stayed till the age of 10 weeks.

For a few days after birth he got a little mother's milk. Otherwise his nutrition was entirely artificial; in the Children's Hospital he was given half-skimmed citric acid milk. He thrived; at the age of 1 month he weighed 2 350 g at his discharge, 10 weeks old, 3 300 g, measuring then 49 cm in length. He presented no particular abnormal features in the hospital, especially no catarrhal phenomena. His temperature was normal throughout his stay in the hospital. There was no icterus, dyspnea or anemia. The Wassermann reaction was negative in the mother as well as in the child (three tests).

*Serum proteins*: in the third week of life: 4.4 % (albumin 3.3 %, globulin 1.1 %); in the fifth week: 5.0 % (alb. 3.9, glob. 1.1); in the seventh week 4.9 % (alb. 3.4, glob. 1.5); in the ninth week 5.3 % (alb. 4.2, glob. 1.1). *Moro and Mantoux*: negative. On discharge the hemoglobin percentage was 83; the red blood count: 4.18 million. *Urine*: no pathological elements. *Blood urea* 26—17 mg %.

On admission to the Children's Hospital the child was given 10 mg K-vital. From the beginning of the second week of life he was given 10 cg ascorbic acid daily; from the beginning of the third week, 4—8 drops of a concentrated vitamin A—D preparation (Adetamin forte) daily; from the sixth week, 10 cg daily, increasing to 10 cg  $\times$  3 daily of an iron preparation (pulvis ferrosi tartratis). Otherwise he was given no medicament treatment. — At the beginning of the ninth week he was given a blood transfusion into the left tibia consisting of 50 cc of blood from his father (child and father belonged to group A). No reaction after the blood transfusion.

At the age of 10 weeks the child was discharged to his home. Here he was given citric acid milk according to the practice of the hospital (100 cc  $\times$  6), ascorbic acid (10 cg daily), adetamin forte (4 drops daily) and iron in the same dosage as above. According to the information given by the mother, the boy was thriving normally until — at the beginning of the thirteenth week — he commenced not taking his food, though he presented no other symptoms (observed only by the mother). — Two days later he died suddenly.

*Autopsy* (University Institute of Forensic Medicine, 241/47). — Weight 2 840 g; length 51 cm. No abnormality of the skin.

*Pleurae*: no effusion, no patches of exudate, but several petechiae on the visceral pleurae.

*Lungs*. — Both lungs markedly changed. The anterior parts showed pronounced acute emphysema. No interstitial emphysema. In the other parts of the lungs, in particular paravertebrally, and equally in both, ex-

<sup>1</sup> The writer is greatly obliged to Dr. A. Rothe Meyer, Chief Physician, for permission to make use of the case record (640/47).

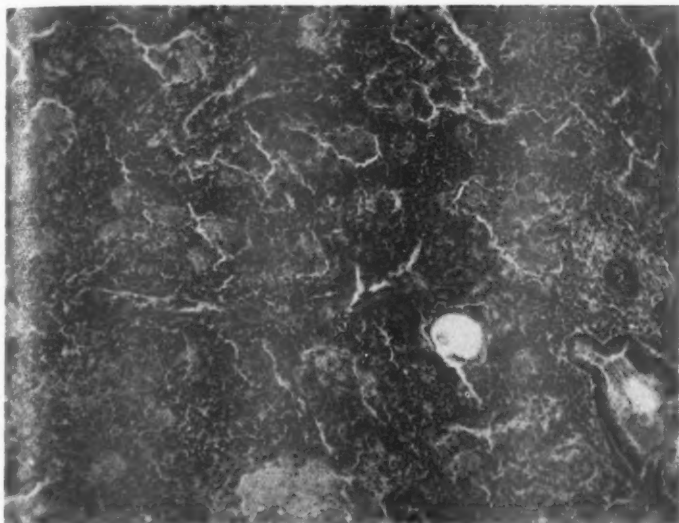


Fig. 1. Interstitial plasma cell pneumonia (case I). Thickened alveolar septa massively infiltrated with mononuclear cells, especially plasma cells. Serous exudate in the alveoli. Bronchial lumen free (100  $\times$ ).

tensive dark-red, partly atelectatic areas were seen, some of them slightly depressed, others slightly protruding. In these areas there was a considerable increase in consistency and marked hyperemia. From the cut surfaces of the posterior parts scanty amounts of a rather viscous, greyish, hardly purulent fluid exuded. No plugs of pus were seen in the bronchioles. A little mucus, apparently slightly purulent, was found in the trachea and main bronchi.

*Bronchial lymph nodes:* slightly enlarged, greyish-red to dark-red in color.

*Other Organs.* — No particular abnormality. In particular, no hyperplasia of the spleen or lymph nodes. No malformation.

*Microscopic Examination.* — In all the sections examined the lungs presented the same picture: the alveolar septa were enormously thickened throughout (Fig. 1), massively infiltrated with close-packed, exclusively mononuclear cells — plasma cells, histiocytes and lymphocytes. Plasma cells of different degrees of maturity made up 80 % of the cells; and a great majority of the plasma cells were mature, typical (Fig. 4). Thick mantles of the same cells enveloped the bronchi and vessels. Pronounced

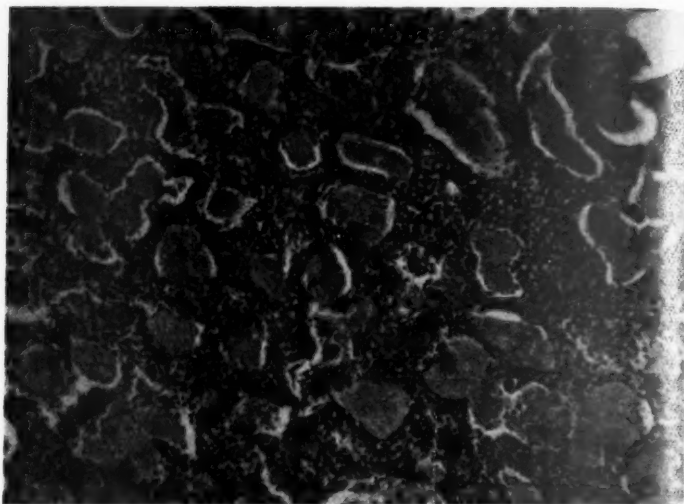


Fig. 2. Interstitial plasma cell pneumonia (case II). The same findings as in Fig. 1 (100 $\times$ ).

hyperemia of the alveolar septa. Nearly all the alveoli were filled with a finely granular serous exudate, which gave no reaction for fibrin (Weigert) or fat (Sudan III). Very few macrophages and no leucocytes were seen in the alveolar exudate. Here and there the alveoli were lined with a low cuboidal epithelium (Fig. 3). The lumina of the bronchioles were free or contained a little exudate of the same appearance as that seen in the alveoli (Fig. 1), with very few leukocytes here and there. — No inclusion bodies were seen in the bronchial or alveolar epithelia. No fibrosis or granulomas, no giant-cells, no areas of necrosis, and nowhere any bronchopneumonic or bronchiolitic changes of the usual type.

Unfortunately, only lung tissue was fixed for microscopy, as the diagnosis was not made before the histologic examination.

*Epicrisis.* — A boy about 2 months premature (weighing at birth 1 450 g), who was thriving well, was suddenly taken ill without prodromal symptoms when nearly 3 months old, refusing to take food, and died suddenly 2 days later. *Autopsy* revealed extensive dark-red, hyperemic, partly atelectatic, areas of increased consistency distributed equally in both lungs, in particular paravertebrally. Apart from moderate hyperplasia of the bronchial lymph nodes no other conspicuous abnormality was seen. Histologic examination of the lungs showed typical interstitial plasma cell pneumonia.

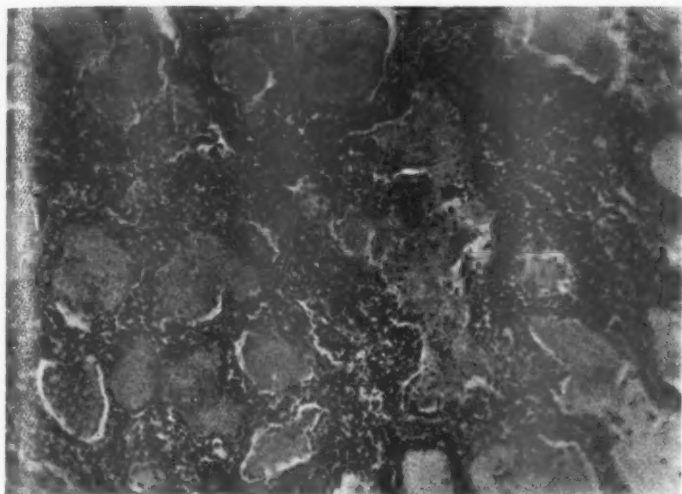


Fig. 3. Interstitial plasma cell pneumonia (case II). Cuboidal lining epithelium in some of the alveoli (100 $\times$ ).

**Case 2.** The child, a boy (twin), was born six weeks before term, weighing 2 000 g and measuring 47 cm in length. Twin No. 2 died one hour after birth. The mother, primipara, was suffering from pulmonary tuberculosis, showing +TB in gastric lavage during pregnancy. After parturition, spontaneous by normal delivery, she was feeling well. At the age of 12 days the child was transferred from the Lying-In Department of the Rigshospital to the Fuglebakken Children's Hospital, Copenhagen, where he stayed for two months. Here he was Calmette-vaccinated at the age of 2 weeks. In the hospital he was given mother's milk (from a wet nurse); after his discharge from the hospital he was given milk mixture. He was continuously given an abundant supply of vitamins A and D, besides iron. After his discharge he was under observation by a Children's Welfare Nurse and a Children's Welfare Center — the last time four days before hospitalization.

At the beginning of the fourteenth week he was admitted to the Medical Department B of the Frederiksberg Hospital<sup>1</sup> for malnutrition,

<sup>1</sup> The writer is indebted to the Chief Physician of the Medical Dep't B. of the Frederiksberg Hospital, Dr. N. R. Christoffersen, and to the chief of the Pathologic Department of this hospital, Dr. L. Heerup, for their permission to make use of this record.

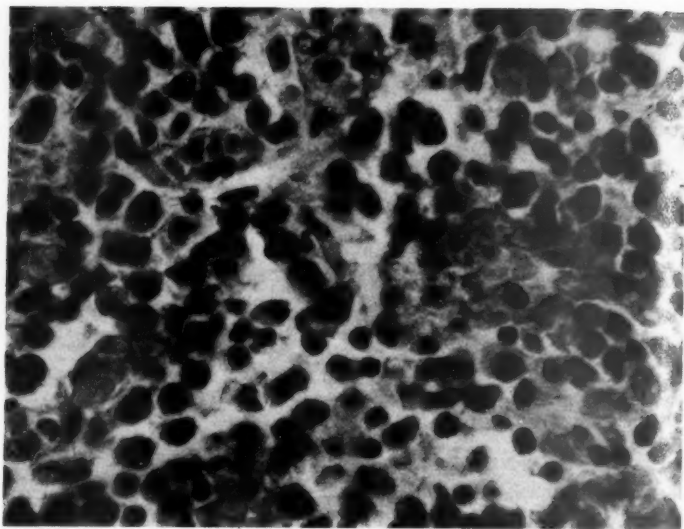


Fig. 4. Interstitial plasma cell pneumonia (case I). Interstitial inflammation reaction. About 80 % plasma cells, some macrophages and a few lymphocytes (750  $\times$ ).

cyanosis and dyspnea. During the last week before admission his appetite had been poor, he had had "difficulty in breathing," and he had been greyish pale. There had been no vomiting, diarrhea, convulsions, nor fever.

*On admission* he was seen to be a small, delicate and emaciated child, greyish cyanotic, with a respiratory rate of 144. No abnormality of the skull, eyes or fauces. No sign of rickets. Auscultation of the heart and lungs revealed no abnormality, nor was any other abnormality found on physical examination. Weight on admission 3 440 g (six days before it had been 3 800 g); three days after admission, 3 500 g; and five days after admission 3 480 g. In the days after his admission he remained greyish pale and dyspneic, becoming cyanotic on crying.

*Roentgenography of the lungs* three days after admission. — In the lower part of the right lung a somewhat spotted and marmorated density, in particular medially, up towards the hilus. The configuration of the lungs was vigorous throughout, though somewhat blurred.

*Temperature.* — On admission it was 36.2°, next morning 37.4°; then 37°—37.6° for the following two days, and on the fourth day after ad-



mission it was  $37.9^{\circ}$ — $37.7^{\circ}$ , on the fifth day  $38^{\circ}$ — $38.5^{\circ}$ , and on the sixth day  $37.9^{\circ}$ — $38.2^{\circ}$ .

The *urine* contained no pathological elements. The *stools* were normal.

*Respiration.* — On admission 144. On the following day 88, two days after admission, 120; three days after, 126; four days after, 132; five days after, 132; six days after, 136.

*Pulse rate:* on admission 140, subsequently between 110 and 160.

*Hemoglobin percentage:* 104.

*Treatment* was instituted from the third day with penicillin, 30 000 units  $\times$  3, and streptomycin, 125 mg  $\times$  4. In addition, the patient was given cod liver oil, glucose-saline, oxygen, and stimulants. But he died on the sixth day after admission, with pronounced cyanosis, increasing respiratory rate, and increasingly superficial breathing.

*Autopsy.* — Small and delicate child with a reddish elevated spot on the left shoulder about 0.5 cm in diameter (Calmette vaccination).

*Pleurae:* smooth and glistening; in particular, no patches of fibrinous exudate.

*Trachea and bronchi:* no secretion; mucosa pale.

*Bronchial lymph nodes:* no enlargement.

*Lungs.* — Rather large, light in color; judging from the surface physematous. But the cut-surfaces in all the lobes showed diffuse, rather light densities, and here the tissue was almost devoid of air, "carnified" throughout. Only a slight amount of non-purulent fluid on the cut-surfaces. No pus in the bronchioles.

The remaining organs, including the central nervous system, presented no macroscopic abnormality, especially no sign of tuberculosis. No enlargement of the spleen.

*Microscopic Examination.* — The *lungs* showed much the same changes as were seen in Case 1 (Figs. 2 and 3). In all the sections the alveoli were filled with "serous" exudate. Plasma cells constituted about 70 % of the cells in the interstitial inflammatory infiltration. Small lymphatic nodules of normal appearance, without plasma cell infiltration, were seen round vessels and bronchi.

*Bronchial lymph nodes* rather small, markedly hyperemic. Some middle-sized germinal centers, with admixture of lymphocytes. The follicular pattern was rather inconspicuous. Some lymphocytes and histiocytes in the sinuses, but no definite sinus reticulosis. Only rather few plasma cells (mature and immature) among the lymphocytes.

*Inguinal lymph nodes* quite small, without germinal centers, showing no abnormality apart from hyperemia — in particular, no plasma cell proliferation.

*Bone marrow* of normal composition, especially no plasma cell proliferation.

*Spleen.* — Marked congestion of the red pulp, with moderate diffuse reticulum proliferation and moderate amounts of immature plasma cells, but nowhere any considerable amount of plasma cells. Follicles rather small, without conspicuous germinal centers.

*Liver and Kidney.* — Acute stasis and slight cloudy swelling. Otherwise no abnormality — in particular, no plasma cell infiltration.

*Brain and myocardium:* no abnormality.

*Site of Calmette vaccination:* a fairly large conglomerate in the subcutis of vaguely defined epithelioid cell granulomas without areas of necrosis and without giant cells.

*Epicrisis.* — A boy (twin), born about six weeks before term, with a birth weight of 2 000 g, was thriving, when, at the age of 14 weeks, he suddenly — without any prodromal symptoms whatever — refused to take his food and became dyspneic. The rate of respiration increased markedly and the patient became cyanotic; finally there was slight elevation of the temperature (maximum 38°). No favorable effect was obtained with penicillin or streptomycin. The patient died two weeks after the onset. On *autopsy* nearly all the lung tissue was found to be consolidated, free from air, with increased consistency. Otherwise no macroscopic abnormality. Histologic examination showed typical interstitial plasma cell pneumonia.

### Occurrence of the Disease

This disease was first described in 1938 (3, 4). It may be that a few previously reported cases (13, 46, 59) of infantile interstitial pneumonia rich in plasma cells have been of the same character. But as some of them were observed in connection with measles (59), or measles together with whooping-cough (13), it seems rather uncertain whether these were identical with the cases described in 1938 and later. The first of the well-described cases reported in 1938 appear to have been observed in 1935 — possibly even as early as in 1928 (46). From 1938 until now a total of about 350 cases of this disease have been published (3, 4, 17, 18, 20, 27, 30, 37, 39, 41, 42, 50, 51, 52, 53).

But the diagnosis was verified by post-mortem examination in only about 150 of these cases.

It was pathologists who reported the first cases of this disease and called attention to it, as its pathology is evidently far more characteristic than its clinical aspects.

Besides the changes in the lungs, two features of this disease stand out conspicuously: 1) it occurs almost exclusively in prematures in their second—third months of life; and 2) apart from a case recently reported from Sweden (30) and the 2 cases reported in this paper, so far the disease appears to have been observed only in German-speaking countries and to have turned up, or become recognized, evidently for the first time about 15 years ago.

These two circumstances have given rise to all sorts of theoretical speculations, more or less subtle. In particular, the question has been discussed whether we here might be faced with a morbid condition resulting from the treatment applied to prematures in the countries mentioned.

On further consideration of these two characteristic features, we find concerning the first one that the disease occurs almost exclusively in prematures in their second—third months of life and that of the 299 reported cases in which it was stated whether or not these infants were prematures, 257, or *about 85 %*, *proved to have been prematures*. In most of the other cases the patients were underweight weaklings, but the disease has been observed also in children born at term with normal weight (50). In a little over 80 % of the fatal cases, death occurred in the second—third months of life, especially in the eighth and ninth weeks. In two cases (3, 20) the illness set in on the first day of life. Otherwise the earliest cases observed occurred in the sixth week of life. In a few cases the onset came in the latter half of the first year, the latest cases reported appearing in the eleventh month of life (3, 4). — The frequency of the disease appears to be independent of sex and season. On the other hand, it is quite evident that some cases have appeared in waves, in the same department and in the same rooms. In some clinics in Switzerland (41, 52) there have been periods in which 40—60 % of the prematures contracted the disease (including the cases of recovery). This might indeed be taken to indicate that, above all, the disease is contagious. But attention has also been paid to the possibility of a reaction of the prematures to a uniform treatment.

It is a very striking fact that all the cases of this disease ob-

served so far — with the exception of 1 case from Sweden (30) and the 2 cases reported in this paper — have occurred in German-speaking countries, namely: 1) Germany, 2) Austria and 3) Switzerland. Within these three countries the reported observations were made respectively in 1) Berlin, Heidelberg, Rostock, Danzig, Halle and Greifswald, 2) Vienna and Graz, 3) Basel, Berne and Lucerne, while, strange to say, no case has been reported from the French-speaking part of Switzerland. Whether a few cases of infantile interstitial pneumonia reported by American (48) and French (8) authors as difficult to classify might have been identical with the disease we are dealing with here is something that cannot be settled on the basis of the reports concerned. Du Pan & Roulet (41) (1946) have gone through all the Anglo-Saxon, Scandinavian, Italian, and Spanish literature on pneumonias in children within the last 10 years without finding any instance of plasma cell pneumonia reported. As both German and Swiss reports on this disease have been cited repeatedly in the British as well as the American literature (*e.g.*, Yearbook of Pediatrics 1941) the absence of reports from the Anglo-Saxon countries can hardly be due to ignorance about the existence of this disease. Moreover, the pathology of the disease is so characteristic that it cannot be overlooked or mistaken for anything else.

### Pathology

*Changes in the Lungs.* — The description given of the changes found in the lungs is almost the same for all the cases reported. A very characteristic point is that the pleurae and bronchi never are affected. Most authors state that all the lobes of the lungs are attacked in the same degree or in particular posteriorly. The lung tissue is described as dark red or greyish-red, frequently similar in consistency and appearance to that seen in indurative syphilitic pneumonia (white pneumonia), with markedly moist cut-surface. The anterior aspects of the lungs are often the sites of acute emphysema, sometimes also interstitial emphysema. Often only the most anterior parts of the lungs contain any air.

Histologically, the changes in the lungs show two characteris-

tic features: 1) a finely granular, serous exudate, almost free from cells, in the alveoli and sometimes in the bronchioles; and 2) massive interstitial inflammatory infiltration of the alveolar septa and in the perivascular and peribronchial connective tissue. In some parts of the lungs this exudate is found in nearly all the alveoli, while only very few alveoli are atelectatic or air-containing. The exudate is quite finely granular, appearing as exudate rich in protein, and strongly reminiscent of the exudate encountered in rheumatic pneumonitis. It gives no reaction for fibrin (Weigert) or fat (Sudan). Still, a few authors (16, 41, 45) state that peripherally in the alveoli this exudate may be slightly sudanophil and present the character of hyaline bands of the same appearance as, for instance, in aspiration pneumonia in the newborn (49), in rheumatic pneumonitis and virus pneumonia. A few macrophages and/or alveolar epithelial cells, in addition to very few neutrophil leukocytes, may be seen in the exudate. Sometimes the alveolar epithelium is cuboidal.

The interstitial inflammatory infiltration, which increases the thickness of the alveolar septa immensely, consists chiefly of plasma cells (50—80 % of the cells). Some of these cells are typical mature Marschalko plasma cells; others present the character of immature plasma cells of the type seen, for instance, in lymphatic tissue during immune reactions (11, 34). This massive plasma cell infiltration is the more striking as otherwise only exceedingly few plasma cells are found in the infantile organism (in the bone marrow, for instance, plasma cells cannot be demonstrated until the second—third months of life and even then only in very scanty amounts (23)). Lymphocytes and macrophages are found among the plasma cells but no leukocytes — neither neutrophil nor eosinophil — nor any mast cells. — One author (UNDRITZ, 56, 57) claims that the dominating cell type in smears is to be interpreted as monocyte. In sections, however, the plasma cell character of the great majority of the cells is so evident that there seems to be no question about their being plasma cells.

*The hilar lymph nodes* are often stated to be enlarged and sometimes more or less infiltrated with plasma cells (41). Hyperplasia of other lymph nodes appears not to have been observed

nor has any microscopic examination been reported of lymph nodes other than those in the hili. On our Case 2 the hilar lymph nodes showed a slight increase in plasma cells, while the inguinal nodes appeared normal.

*Spleen.* — Moderate enlargement of this organ has been reported in some cases (29) and sometimes an increase in its plasma cell content (30, 41).

The *bone marrow* shows no abnormality (41) or a very slight increase in plasma cells (30). The *other organs* appear to have been examined in only a few cases. LINELL (30) found small plasma cell infiltrations in the liver and kidneys in his case, but it is to be mentioned that this patient was also suffering from dermatitis in addition to interstitial pneumonia.

From the few systematic histologic examinations of the reticulo-endothelial organs it seems justifiable to conclude that the process in the lungs is *no* part of any systemic disease.

The *central nervous system* appears to have been examined only in very few cases. In a few of these an inflammatory infiltration was reported observed in the mesencephalon (50), which the author took to signify that the disease might be due to a neurotropic virus, while in other cases no abnormality was observed (18).

### Clinical Aspects

The clinical picture (29, 38, 39, 40, 41, 42, 50, 52) is far less characteristic than the pathologic and it has been suggested (38) that only those cases are to be recognized in which autopsy has verified the diagnosis. Gradually, however, so many cases have been diagnosed *in vivo* and later verified by autopsy that it seems practicable to make the diagnosis on the clinical signs and X-ray findings. From some clinics where many prematures are cared for it is even stated that once the clinical picture has become familiar, it is so characteristic that the nurses are able to make the diagnosis (50).

The initial stage is associated neither with catarrhal phenomena nor with cough or fever. Only the general condition is affected somewhat: the patient looks poorly, refusing to take food,

is languid, though sometimes restless, and in particular becomes increasingly dyspneic. This condition goes on for some days — up to a couple of weeks — before the fully developed clinical picture is seen, characterized by pronounced dyspnea with dilated nostrils, retraction of the epigastrium, cyanosis and exceedingly frequent respiration (80—120), but no cough. Often death sets in, under suffocation, a few days after the clinical picture has developed fully, with such an excessive dyspnea as to remind of tension pneumothorax (37). In surviving patients the acute dyspneic stage may last for 5—10 days (41).

*Auscultatory changes* are often completely absent or very scanty (a little crepitation, suggestion of bronchial respiration, and paravertebral dullness).

*Temperature.* — Even in the dyspneic stage the temperature rises but very little, to about 38°. — Often the *weight curve* is surprisingly unaffected, and it is reported sometimes even to rise a little during the illness (tendency to edema?).

*X-ray Findings.* — (29, 39, 41, 50, 52). The roentgenographic changes in the lungs are said sometimes to be so characteristic that the disease may be diagnosed prior to the serious stage of dyspnea. Delicate scattered bilateral shadows and spots, arising from the parahilar regions, increase in extent and intensity, and in the terminal phase they may become confluent, presenting a complete opacity of both lungs (41).

*Rate of Respiration.* — The pronounced rise in the respiratory rate, from the normal value of 40—60 in prematures up to 80—120, is stated to be very characteristic. TOBLER (52) considers this symptom to be the most reliable for an early recognition of the diagnosis.

*Blood Picture.* — (29, 39, 41, 52). There appears to be no absolutely characteristic blood picture in this disease. In some cases the white blood count is normal, while in others it is as high as 20 000—25 000; neutrocytosis (41) is seen in some cases, lymphocytosis (39) in others. Plasma cells are not seen in the peripheral blood (29, 39). The *sedimentation rate* (27, 29, 41, 52) is sometimes normal, sometimes slightly increased (about 20 mm) and greatly increased in a few cases (52) (up to 90 mm). — The behavior of

the *serum proteins* will be mentioned under "Pathogenesis and Etiology."

As to the *duration* (29, 36) of the disease, owing to the uncertainty of the clinical symptoms the statements are highly variable and uncertain. In the fatal cases the duration of illness has varied from 1—10 days up to 3 weeks. On the basis of their experiences from a fairly large material of survivors, DU PAN & ROULET (41) think they are able to distinguish between an incubation stage of about 15 days, an acute phase of 5—10 days, and a restitution phase of 2—4 weeks. — Only in very few cases (38) has death occurred without preceding signs of illness. In this connection it is to be mentioned that in an autopsy material from the University Institute of Forensic Medicine, Copenhagen, comprising 135 cases of sudden or unexpected deaths in children under one year during the period of 1946—1949, only one instance of plasma cell pneumonia (Case 1) was observed.

Owing to the difficulty of the clinical diagnosis, the *lethality* of the disease is difficult to estimate with certainty, but presumably it is rather high. DU PAN & ROULET (41) state that in their material the lethality was as high as 66 %, but after the introduction of short wave therapy it was only 13 %. TOBLER (52) states the lethality to be about 15 %.

### Pathogenesis and Etiology

A number of hypotheses have been advanced concerning these two aspects, but both are still obscure.

Roughly, these theories fall into the following groups:

1. Aspiration pneumonia ("Pflugeschaden").
2. Infection.
3. Age-constitutional factors in prematures and weakly children, including in particular the behavior of the serum proteins.

The possibility of any systemic affection appears to be excluded — only the lungs being affected — and only one author (13, 16) appears to have had a tendency to reckon with that possibility.



1. *Aspiration Pneumonia*. — Aspiration of food, etc., has been assumed by several authors (17, 29, 45) to be the essential etiologic factor — owing to insufficient swallowing and coughing reflexes in weak infants. But aspiration pneumonias, including lipid pneumonia, (19, 24, 35) present an entirely different pathologic picture.

2. *Infection*. — Most authors (4, 27, 41, 50, 53) assume some infection to be the cause of this disease. But blood cultures (29, 41) and cultures from the lung tissue (4, 20, 38, 41, 42) have furnished no evidence in support of the theory about bacterial infection. Syphilis can be excluded as an etiologic factor, and no convincing facts have been found to the effect that here we might be faced by a virus pneumonia. Cold agglutinins have not been demonstrated in the blood (53), and so far animal experiments have not furnished any evidence in support of a virus infection (41). Furthermore, the pathologic picture of this lesion differs, especially in its lack of bronchiolitis, from the usual picture of virus pneumonia (primary atypical pneumonia (1, 2, 21) — even though many plasma cells may be seen in this form of pneumonia (21) and, for instance, from pneumonia of measles (12, 22, 33, 59). Nor have inclusion bodies in the epithelial cells hitherto been demonstrated in plasma cell pneumonia (LINELL (30) and the 2 cases reported in this paper).

Another argument advanced *against* the infection theory is the circumstance that the children with interstitial plasma cell pneumonia show catarrhal phenomena prior to the manifestation of the pneumonia only very seldom, and that this lesion runs its entire course almost without any elevation of the temperature.

One fact, on the other hand, speaks *in favor of* an infectious origin, namely: that many cases made their appearance in waves in the same department and the same rooms (38, 41, 50, 52), and that the lesion seems to be a nosocomial disease (41).

As to the possibility of this disease being of *allergic character*, it is to be mentioned that the histologic changes here observed differ from the allergic tissue reaction usually observed, even though the many plasma cells are suggestive of intensive antigen-antibody reactions taking place in the lung tissue.

3. *Age-Constitutional Factors.* — Undoubtedly such factors and special conditions particular to the organism of premature and weak children are contributory to the characteristic pathologico-anatomical features that seem to be quite specific of this lesion.

In particular, attention has been focused on the behavior of the *serum proteins* in prematures and weak children belonging to the age group here concerned.

As is well known, GYÖRGY (25) has made a statement that has been cited frequently (4, 16, 27, 41, 45) to the effect that in the infant, as far as serum proteins are concerned, the second—third months of life represent “der biologische Grenzpunkt der neugeborenen Periode,” as the “embryonal serum albumin-globulin relation with the relative hyperalbuminemia” at this juncture disappears. On this account, several authors (4, 16, 27, 29, 41, 42, 51) have discussed the possibility that the predominance of interstitial plasma cell pneumonia in this age group depends somehow on the altered relation of the serum protein fractions.

But a review of the more recent literature concerning serum proteins in infants appears not directly to confirm the claim that just the second—third months of life represent a turning point for the serum proteins.

In later years several investigations have been published on the serum proteins in normal newborn children and infants (9, 10, 27, 28, 32, 36, 40, 43, 44, 54, 55) as well as in prematures (9, 28, 32, 44 a, 55) and fetuses (9, 36). Several of the materials, however, comprise but few examinations and include no determination of the protein fractions. Furthermore, the results are not quite clear-cut.

It appears as if fetuses and normal prematures give considerably lower values for total protein as well as for albumin and globulin, but a higher albumin/globulin ratio than do full-term babies. This applies, at any rate, to the prematures, whereas such studies carried out on fetuses have been exceedingly scanty. Furthermore, normal full-term babies appear to behave in the same way in relation, for instance, to infants of 6 months. As to the physiologic changes in the ratio of the protein fractions in

normal infants during the first months of life, however, the materials investigated have been very small, and the results obtained have been difficult to estimate because of the scanty number of tests within the individual age groups. From the most comprehensive and best selected material (TREVORROW and collaborators, 54) for elucidation of this matter it seems evident that after the *albumins* have kept at an average level of 3.79 % ( $\pm 0.33$ ) during the first month of life, they then show a gradual rise reaching the adult level some time between 6 and 12 months of life, most of them already at an age of about 6 months. For the *globulins* the average value at birth and in the first week of life is 1.66 % ( $\pm 0.29$ ). Between the first and fifth weeks of life the globulin values fall to 1.31 % ( $\pm 0.25$ ), after which they remain at about this level to the age of 6 months. From now on there is a quite gradual rise in the serum globulin until the age of about 4 years, when the adult level is reached.

As to the *fibrinogen*, the values are stated to lie a little higher and show more variation in the first 4 weeks than later on. From the fourth week no significant changes are seen in the values.

Largely, the findings recorded in the other materials investigated (9, 10, 43, 44) appear to be in keeping with those mentioned above. — So, on the basis of the findings obtained by ordinary fractionation, it appears as if the above-mentioned "turning point" for normal children lies at the age of about 6 months rather than 2—3 months. — Nor do the findings obtained in the cases of normal prematures seem to indicate that the second—third months of life represent any turning point in the albumin/globulin ratio (32).

However, mention may be made in this connection of some highly interesting *electrophoretic* studies on serum proteins in infants, especially the behavior of the gamma globulins reported by MOORE and collaborators (36). The albumins are stated to increase quite gradually from birth up to the age of 10 months (this investigation includes no older children). The alpha and beta globulins increase considerably in the first month of life, after which they remain almost unaltered. For the gamma globulins the percentage is relatively high at birth (17—23 %), higher than

in the mother. Then it falls considerably during the first 3 months (to a level of about 5—7 %) after which it shows a quite gradual rise up to the age of 10 months. The authors emphasize that the fall in gamma globulins within the first month of life corresponds to the disappearance of the maternal antibodies that was to be expected in the serum of the child (47).

This circumstance that at the age of about 3 months the child possesses a lower antibody-globulin concentration in the blood than at any other time of life appears quite likely to be a contributory factor in the predominance of interstitial plasma cell pneumonia at this juncture, and it seems reasonable, moreover, that prematures and weak children have more difficulty in producing antibodies than have normal children. — In view of the unquestionable relation between plasma cells and globulins (5), especially antibody globulins (6, 7, 11, 23), it will be appropriate in this connection to emphasize the well-known fact that no plasma cells at all are encountered in fetuses and normal infants, and that even scanty amounts of plasma cells cannot be demonstrated in infants before their second—third months of life (23) — at the juncture when the child itself will have to produce its own antibodies.

As to the *behavior of the serum proteins in children with plasma cell pneumonia*, only few studies have been reported so far (18, 27, 40). FREUDENBERG (18) and NITSCHKE (40) found no definite abnormality, whereas HENNIG (27) states that in all the (16) cases examined by her she found hypoproteinemia with a distinct decrease in albumins and a slight rise in globulins. In some experiments with cantharidine she found the protein value for the contents of the cantharidine vesicles to be higher in prematures with plasma cell pneumonia than in normal prematures. On the basis of her various findings, HENNIG then discusses the possibility that lowered capillary resistance, resulting in diffusion of plasma into the tissues, might be a pathogenetic factor, so that a pulmonary edema would elicit the interstitial inflammatory reaction. — In this connection it is also to be mentioned that the theory has been advanced that transfusions (31) given to prematures might, by way of pulmonary edema, play some rôle as a patho-

genetic factor in plasma cell pneumonia. As a matter of fact, in many of the published cases of interstitial plasma cell pneumonia the infants had been given blood transfusion.

Thus the question concerning the pathogenesis and etiology of this disease is still uncertain. As early as 1938 BENECKE (4) stated that undoubtedly the appearance of the protein-rich edema in the alveoli is the primary phenomenon, and that the interstitial inflammatory process is a reaction to the edema. And it seems not unlikely that BENECKE may be right in this. At any rate, the interstitial inflammatory infiltration with the numerous plasma cells may be taken to indicate that an intensive antigen-antibody reaction is taking place in the alveolar septa — presumably because some antigen is being absorbed from the alveoli. Indeed, it may be that *both* an infection, most likely, I think, with a virus, and the special constitutional phenomena (hypoproteinemia and hypogamma-globulinemia with the resulting decrease in the resistance) contribute to the production of the characteristic changes in the lung.

### Treatment

Sulfa preparations are stated by some authors (29, 38, 40) to have no effect whatever on cases of this disease, while they are recommended by others (27, 41, 52) for prevention of complications. Nor does penicillin appear to have any effect (53). In one of our patients (Case 2) no effect was obtained from treatment with penicillin and streptomycin given simultaneously. Short wave therapy is claimed by some authors (29, 38, 41, 52) to be effective. Still, as the clinical diagnosis presumably is often uncertain, it seems difficult to appraise the effect of this therapy. In addition, administration of oxygen and stimulants is recommended.

### Summary

A report is given of 2 cases, verified by autopsy, of interstitial plasma cell pneumonia in prematures, aged 12 and 14 weeks, respectively, who died after two days and two weeks of illness. In this connection a survey is given of the occurrence, pathology,

clinical aspects and treatment of interstitial plasma cell pneumonia.

It is a striking fact that 85 % of the published cases of this disease, which was first recognized about 15 years ago, have occurred in prematures, especially in the second—third months of life, and that the disease hitherto appears to have been observed only in Germany, Austria, Switzerland and the Scandinavian countries.

The theories advanced concerning the unknown etiology and pathogenesis of the disease are reviewed. It seems most likely to involve an infection (with a virus?) which, on account of particular conditions (hypoproteinemia, hypo-gamma-globulinemia, and low resistance?) gives rise in the organism of premature and weak infants to the very characteristic changes found in the lungs.

### Résumé

On fait un rapport de deux cas, vérifiés par l'autopsie, de pneumonie interstitielle plasmocytaire chez des enfants nés avant terme, âgés de 12 et de 14 semaines respectivement, qui sont morts après deux jours et deux semaines de maladie. A ce sujet, l'auteur fait une étude de la fréquence, de la pathologie, des aspects cliniques et du traitement de la pneumonie interstitielle plasmocytaire.

C'est un fait frappant que 85 % des cas publiés de cette maladie, qui n'a été reconnue qu'il y a environ 15 ans, se sont produits chez des enfants nés avant terme, spécialement au cours du deuxième—troisième mois d'existence, et que jusqu'ici la maladie semble n'avoir été observé qu'en Allemagne, Autriche, Suisse et dans les pays scandinaves.

On fait un examen des théories présentées concernant l'étiologie et la pathogénie inconnues de la maladie. Il semble très probable qu'il s'agit d'une infection (par un virus?), qui, par suite de conditions particulières (hypoprotéinémie, hypo-gamma-globulinémie et faible résistance?), provoque dans l'organisme d'enfants nés avant terme et faibles les changements très caractéristiques constatés dans les poumons.

### Zusammenfassung

Bericht über zwei durch Sektion verifizierte Fälle von interstieller Plasmazellenpneumonie bei Frühgeburten 12 bzw. 14 Wochen alt, welche nach 2 Tagen resp. 2 Wochen starben. In Zusammenhang damit werden Frequenz, Pathologie, Klinik und Behandlung der Krankheit besprochen.

Es ist auffallend, dass 85 % der bis jetzt veröffentlichten Fälle, dieser erst seit etwa 15 Jahren beobachteten Krankheit, Frühgeburten betrafen, besonders im zweiten und dritten Lebensmonat. Die Krankheit ist bis jetzt nur in Deutschland, Österreich, Schweiz und den skandinavischen Ländern beobachtet worden.

Die Theorien der unbekannten Ätiologie und Pathogenese werden besprochen. Wahrscheinlich handelt es sich um eine Infektion (mit einem Virus?) welche auf Grund spezieller Verhältnisse (Hypoproteinämie, Hypo-gamma-globulinämie und geringem Widerstand?) bei frühgeborenen und schwachen Kindern die charakteristischen Veränderungen der Lungen hervorruft.

### Resumen

Se informa acerca de dos casos, verificados por la autopsia, de neumonía intersticial de células del plasma en niños nacidos prematuramente, de una edad de 12 a 14 semanas respectivamente, que se murieron después de dos días y dos semanas de enfermedad.

A este respecto, el autor hace un estudio de la frecuencia, patología, aspectos clínicos y tratamiento de la neumonía intersticial de células del plasma.

Es un hecho sorprendente que el 85 % de los casos publicados de esta enfermedad, que no ha sido reconocida hasta hace unos quince años, hayan ocurrido en los niños prematuros, especialmente en el curso del segundo o el tercer mes de existencia, y que hasta ahora la enfermedad no parece haber sido observada más que en Alemania, Suiza, Austria y los países escandinavos.

Se hace un examen de las teorías presentadas concerniente a la etiología y la patogenia desconocidas de la enfermedad. Parece muy probable que se trata aquí de una infección (¿por un virus?) que a consecuencia de condiciones particulares (¿hipoproteinemía, hypo-gamma-globulinemia y débil resistencia?) provoca en el

organismo de los niños prematuros y débiles los cambios muy característicos comprobados en los pulmones.

#### Addendum in the proof.

Since this paper was sent to the Editor several other cases of interstitial pneumonia have appeared, among others, in the Scandinavian countries.

Thus 3 additional cases, all verified on autopsy, have been observed in Copenhagen (two of them will be published in *Acta Pædiatrica* by Dr. Th. Walther, the third one observed at the University Institute of Pathology).

At the 9th Scandinavian Pathology Congress in Helsingfors, June 1950, A. K. AHVENAINEN reported that he had observed 44 autopsy cases in Helsingfors during the last few years; and O. JÄRVI had observed 10 autopsy cases in Åbo.

From Germany, moreover, 271 cases (60, 63, 64, 65) have been reported — though an account of the autopsy findings is given only in a few of them. The cases came respectively from Rostock, Munich, Bremen and Frankfurt a/Main.

In a number of cases Weisse (65) inoculated animals with venous blood and secretion from the nose and throat of living patients and with blood and lung tissue removed shortly post mortem from patients who died of this disease. In mice and guinea-pigs, which under ether anesthesia had aspired the material mentioned, interstitial pneumonia developed in many cases, and this lesion could be transmitted through several animal passages. Further the author thinks she has been able with the same technique to demonstrate carriers of the infection among the surroundings of the sick children. On the basis of her findings, the author concludes that interstitial plasma cell pneumonia is produced by a pneumotropic virus.

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FROM THE DEPARTMENT OF ANATOMY OF THE UNIVERSITY OF HELSINKI (CHIEF: PROF. NILO PESONEN, M. D.) AND THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI (CHIEF: PROF. ARVO YLPPÖ, M. D.)

## On Changes in the Capillary Vascularity of the Hypophysis in the Human Foetus

by

KALEVI NIEMINEVA

The circulation of the blood in the hypophysis has been described by many workers (POPA and FIELDING, WISLOCKI and KING, GREEN and HARRIS, etc.) who have emphasized the important part played by the hypophysio-portal system in the endocrine function of the pars distalis. They have also observed that the blood vessels of the pars distalis and the neural lobe are independently apart of each other. STEVENS has investigated the capillary vascularity of the component parts of the hypophysis of the cat, and MORIN has studied the supply of blood vessels to the hypophysis in the dog and described the types of the capillaries of the different parts. I have not found any paper on the quantitative development of the capillary network in the different parts of the hypophysis during the foetal period, either in animals or humans. In order to understand the functions of the hypophysis properly, knowledge of the development of the capillaries is important, and I have considered it useful to investigate, as far as possible, this part of the problem of the blood circulation in the hypophysis.<sup>1</sup> It must be stated that in human prematures MALI and RÄIHÄ have observed a generally poor development of the capillaries and ascribed to it many of the differences in the life activity of prematures. On the other hand, the research of CRAIGIE and PETREN clearly demonstrated that an increase in the capil-

<sup>1</sup> Dr. C-E. Râihä, M. D., has encouraged me to make this investigation.

lary network takes place parallel with a growth in the activity of the organs.

Of the above investigations I shall refer more explicitly only to the works of STEVENS and MORIN, as they bear more closely upon my own. In her work STEVENS used the injection method and to fill the capillary network applied a pressure somewhat greater than the normal blood pressure. Her material comprised 22 full-grown cats, of which she selected 10 male specimens for more thorough research. She measured the lengths of the capillaries per 100 cu  $\mu$  and the diameters of the capillary vessels in the different parts of the hypophysis. The following may be quoted from her results.

"The anterior lobe of the hypophysis of the male cat is more richly supplied with blood than the posterior lobe, the ratio of their vascularity in terms of the volume of the vessels in a unit volume of tissue being 6 : 1. The average diameter of the vessels in the anterior lobe is twice that of those in the posterior lobe.

The posterior lobe compared with centers in the brain of the rat has a supply approximating that of the nucleus motorius VII.

The pars intermedia is relatively very poor in capillaries, while the diameter of the vessels is the same as that of the posterior lobe vessels.

The pars tuberalis is richly supplied with blood sinusoids of a diameter even larger than that of those of the pars anterior."

In his work MORIN used the injection and staining methods. In the statistical section he observes that in the dog the capillaries are largest in the pars distalis, where their diameter on the average is 14  $\mu$ . The corresponding figures for the pars tuberalis is 10  $\mu$  and for the neural lobe (posterior lobe) 6  $\mu$ .

According to AREY the human hypophysis receives its characteristic macroscopic shape and structure in the third and fourth foetal months. For this reason I have included this foetal period in the preliminary stage of my own investigations. With regard to the general development of the hypophysis it may be said that its relative weight, i.e. its weight in relation to that of the whole body, decreases from the second foetal month on (LUCIEN and GEORGE).

### Material and methods

As material for the investigation about 60 human fetuses were used, ranging in weight from 100 grams to that of a foetus born at full term. In assessing the final results, however, only 12 fetuses were taken into account. The fetuses were given by Prof. A. Turunen of the Helsinki Women's Clinic.

The fixation and staining was done according to SJÖSTRAND's original benzidine method. In the case of the larger fetuses the fixation in 10 % formalin took place by stages. In the first stage the skull was opened, while in the second the cerebrum was dissected out and then the hypophysis carefully removed. The autopsy and ensuing fixation often took place immediately after death (therapeutic abortion) and at the latest within 48 hours of death, the fetuses having been kept in a refrigerator. Serial sections were cut in thicknesses of 20—50—100  $\mu$ . In assessing the final results only the last-mentioned thickness was used.

An advantage of the SJÖSTRAND method is that the red cells are stained in the vessels so that no delicate capillaries are injured, a risk which may be present when injecting undeveloped blood vessels of fetuses, as MALI and RÄIHÄ found out with prematures. On the other hand, DRUMMOND, examining the brains of a leopard frog, showed that in respect to the capillaries the results of both methods are practically equal. Even with this staining the principal parts of the hypophysis, the pars distalis, the neural lobe, the pars intermedia and the pars tuberalis can on the whole be easily differentiated one from the other.

In the case of humans we are naturally not always in a position to choose for anatomic investigation the best possible research working conditions, as for instance in this work vasodilatation by means of chemicals. In fact, the staining was not successful in all cases and on the strength of a quick histologic examination half of the specimens were discarded.

In the case of 30 fetuses a more accurate measurement of the capillary network was undertaken. Only the capillaries of the pars distalis and the neural lobe were measured, as these components of the hypophysis of even the smallest fetuses are large enough to warrant sufficient accuracy in measurement. The length of the capillaries of the specimens was measured by projecting the picture (magnification  $\times 200$ ) on paper and dividing it into squares of 25 cm<sup>2</sup> each, in which the vessels were drawn.

The number of the squares of each component of the gland studied varied from 40 downwards, depending on the size of the component. Naturally the measurements of one and the same component were made from sections all of which were 100  $\mu$  in thickness. From the results obtained the average value was calculated. In the respective areas the dia-

meters of the least 50 capillaries were measured (Ocular net micrometer, Nochet  $\times 12$ , magnification  $\times 480$ ) and the average value was calculated.

The capillary length was calculated in centimeters per cubic millimeter as done by LINDGREN in Sweden in his investigations of the capillary network of the cerebral cortex in man. In accordance with the method he followed to convert the measurement of the capillary from the two-dimensional value to a three-dimensional value, the resultant measurement was multiplied by  $\sqrt{2}$  (in the sections the course of the capillaries varies from running perpendicular to the microscope's optic axis to parallel with it). This was done in order to obtain an approximate point of comparison between this work and his values. His sections were 200  $\mu$ .

The best picture of the number of capillaries in an organ is given by the volume of the capillary net in a unit volume of tissue. The volume of the capillary network is obtained by using the measurements for the lengths and diameters obtained for the capillaries.

In the final table (Table 1) only 2 foetuses, the capillaries of which were the most fully stained, were approved for each weight class. It must be observed that this best eliminates the possibility of loss of blood from the capillaries due to unsuccessful removal of the hypophysis or some other mishap in preparation, as well as any lack of blood due to physiologic causes.

As the object of the investigation was to compare the density and the quantity of the capillary network during the different stages of the foetal period when the relationship of the values denoting density is of decisive importance, I did not consider it necessary to make any correction for shrinkage. On the other hand, there is reason to recall that the shrinkage during the foetal period changes at least to a minor degree, along with the decrease of moisture in the tissues. Moreover, the parts of the hypophysis, originating from two different layers, naturally react differently to shrinkage. I consider nevertheless that the possibility of unequal shrinkage should not alter the results of this work, because every effort has been made to attain as great uniformity as possible in the autopsy, fixation and staining.

Finally I wish to stress that all the figures supplied by me be regarded as relative values, i. e. they are only significant as a criterion for comparing them to each other within the limits of the present study.

### Observations

A glance at Fig. 1 shows at once that a general idea of the relationship between the vascularity of the pars distalis and the neural lobe may be obtained as early as the middle of the foetal

Table 1.

Sex	Foetuses			Pars Distalis			Neural Lobe		
	Number	Body Weight, gm	Body Length, cm	Capillaries in cm per cubic mm	Average Diameter	Volume in cu. mm of Capillaries per cu. mm Tissues	Capillaries in cm per cubic mm	Average Diameter	Volume in cu. mm of Capillaries per cu. mm Tissues
♂	(No. 57)	120	17	53.3	11.3	0.052	14.9	6.1	0.0042
♀	(♂ 87)	170	21	48.5	12.9	0.063	14.2	6.4	0.0045
♀	(♂ 112)	285	23	50.9	11.2	0.050	13.7	7.5	0.0061
♀	(♂ 74)	330	27	50.2	12.5	0.062	13.8	7.2	0.0056
♀	(♂ 97)	575	30	50.1	15.8	0.098	12.6	8.9	0.0078
♀	(♂ 50)	800	36	49.9	15.2	0.091	12.5	6.7	0.0044
♀	(♂ 53)	1 000	40	52.3	14.0	0.081	14.4	8.1	0.0073
♀	(♂ 106)	1 510	40	52.2	15.4	0.097	18.9	9.2	0.0126
♀	(♂ 69)	2 480	46	59.0	19.3	0.172	17.8	11.9	0.0197
♀	(♂ 214)	2 730	50	54.1	16.6	0.117	23.0	10.3	0.0192
♀	(♂ 223)	3 320	53	57.9	20.5	0.191	—	—	—
♀	(♂ 140)	3 630	52	66.1	21.8	0.246	—	—	—

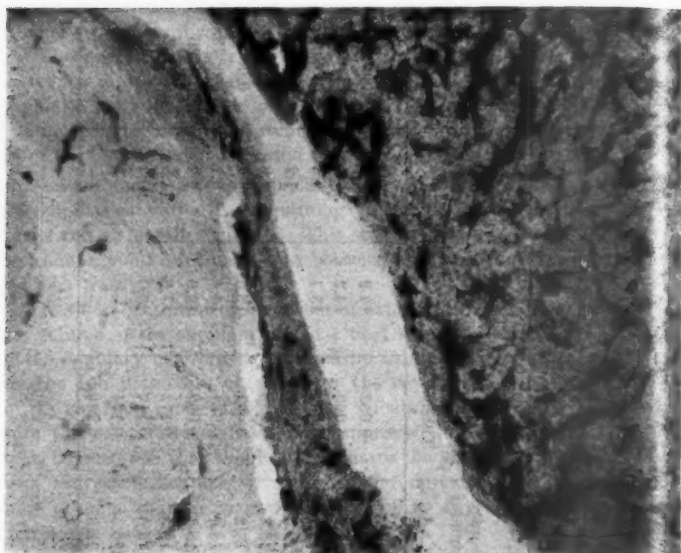


Fig. 1. Photomicrograph of hypophysis in horizontal plane. Human foetus weighing 330 gm (♀). On the right, pars distalis, in the center, pars intermedia, on the left, neural lobe. Magnification  $\times 85$ . Section at 100  $\mu$ .

period. The table shows that in this phase the ratio of the capillary lengths in volume units in these regions is nearly 3—4 : 1, the vascularity of the pars distalis being clearly greater. The ratio of the diameters is 2 : 1 and the ratio of the capillary volumes in the same tissue unit roughly 15 : 1—8 : 1. In the latter half of the foetal period a distinct development of the capillary networks takes place (Fig. 2). The growth in the length of the capillaries in the pars distalis region is less (c. 10 %—30 %) than in the neural lobe (c. 40 %). The diameter of the capillaries in both of these components of the hypophysis increases by almost the same amount, this increase in growth being, however, somewhat greater in the case of the neural lobe. The diameter increases during the period under investigation by about  $3/4$ .

The best measure of the amount of blood in an organ is the



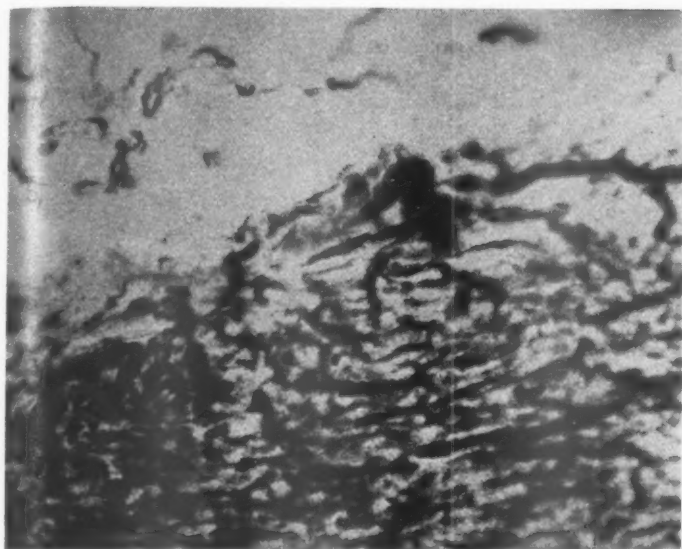


Fig. 2. Photomicrograph of hypophysis in horizontal plane. Human foetus weighing 2 480 gm ( $\delta$ ). Light part above is neural lobe, dark part below is pars distalis. Magnification  $\times 85$ . Section at 100  $\mu$ .

capillary volume of a tissue unit. The growth of capillary volume is clear and perceptible. This is discernible from microphotographs 1 and 2. According to the table, in the region of the pars distalis the capillaries grow, even at a cautious estimate, more than double fold during the latter half of the foetal period. The corresponding growth in the neural lobe is still greater, or in volume per unit of tissue an increase of more than four times.

From the illustration (Fig. 3) it is seen that the density of the capillaries in the region of the pars intermedia is almost as great as in the pars distalis, at any rate greater than in the neural lobe. This phenomenon can be observed in all the specimens studied. Clearly this is question of a local network and not of vessels conveying blood to or from any other parts.

The capillary network in the region of the pars tuberalis ap-

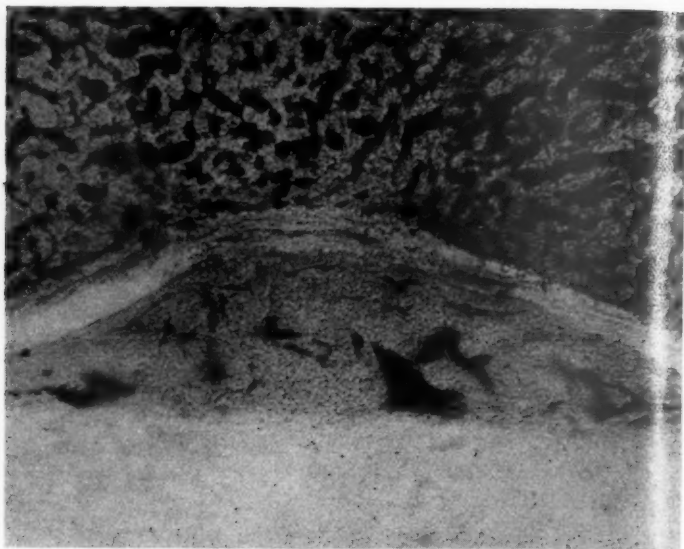


Fig. 3. Photomicrograph of hypophysis in horizontal plane. Human foetus weighing 2 730 gm (♂). In center, pars intermedia. Magnification  $\times 85$ . Section at 100  $\mu$ .

pears at least in large fetuses to be of nearly the same character as in the region of the pars distalis. Observations of the pars distalis are made more difficult by the presence of the portal sinusoids, the diameters of which are naturally much greater than those of a capillary network that is separate and local. In microphotograph (Fig. 4) large portal sinusoids are visible in cross section.

From a study of the specimens it is difficult to give an unreserved opinion on the development of the capillaries of the two last-mentioned parts of the hypophysis; from the observations made it might, however, be stated that the development is the same as in the case of the pars distalis.

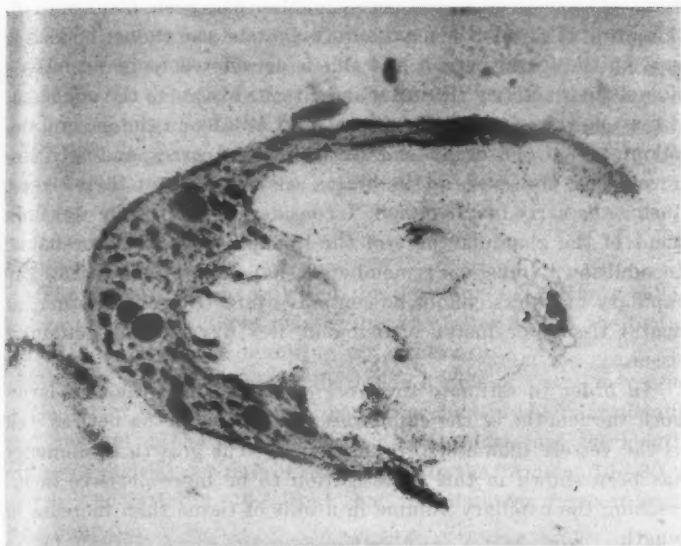


Fig. 4. Photomicrograph of hypophysis in horizontal plane. Human foetus weighing 800 gm (♀). On the left appear bloodvessels in cross section. They are sinusoids of the pars tuberalis. Magnification  $\times 50$ . Section at 100  $\mu$ .

### Discussion

A distinct development of the capillaries of the chief component parts of the hypophysis takes place from the fourth month of the foetal period to its end. The observations of MALI and RÄIHÄ on the general undeveloped state of the capillaries of pre-matures is thus confirmed in the case of the hypophysis. The later increase in their function is relatively greater in the neural lobe than in the region of the pars distalis. On the strength of this it may be considered that the glandular part of the hypophysis develops more rapidly during the early phase of the foetal period and commences its action earlier than the neural component. This early activity of the hypophysis, especially the glandular part, would be warranted by the relatively great weight of the gland in the

early phase of the foetal period, which has been mentioned in this work. The relative maximum weights of the endocrine glands vary in the foetal period, and this is considered to be an indication of their activity (EKHOLM and NIEMINEVA). On the one hand, it may be thought that the neural part is later in the general development of the organ and its capillaries correspondingly less developed. However, as the brains are relatively at their largest during the early foetal period, I consider that an early development of the glandular part of the hypophysis is more probable. In addition it must be remembered that in different tissues the capillary networks cannot be compared directly to each other, as neural tissue for instance, demands less oxygen than glandular tissue.

In order to estimate the working capacity of the capillaries both the lengths of the capillaries (= density of the net) as well as the vessels' diameters are important. The growth in diameter has been shown in this investigation to be more decisive in increasing the capillary volume in a unit of tissue than increase in length.

In comparing the results with those of STEVENS and MORIN obtained from animal specimens, similar ratios have been ascertained. STEVENS gives the relation of the capillary volume in a unit of tissue between the pars distalis and the neural lobe as 6 : 1, whereas in this work the said ratio in the middle of the foetal period is 15 : 1—8 : 1, diminishing in the latter half of the period to 8 : 1—6 : 1. According to MORIN the relation of the diameters of the capillaries in the same parts was 2 : 1, the same as in the present work.

For the pars intermedia there is a difference between the observations made in the present work and those of STEVENS. She found fewer capillaries in this region. In the present work the vascularity of the pars intermedia is similar to that of the pars distalis (STEVENS' adult cats). Because of the minute size of the pars intermedia it is very difficult to say how much its capillaries develop during foetal life. During foetal life the pars intermedia is relatively larger than later on. It is possible that its rich vascularity indicates an important function at this stage of life.

LINDGREN, whose methods perhaps can be compared with my own, ascertained that the length of the capillaries in the cerebral cortex is 10—30 cm/cu mm and the average value 20 cm/cu mm. He expressly emphasizes that his values are relative; absolute values are to be taken with reserve. The capillary network of a newborn infant's neural lobe is of approximately the same average density as the capillaries in the cerebral cortex of an adult man.

### Summary

The author has investigated the development of the capillaries in the hypophysis of man during the latter half of the foetal period and made the following observations.

1) The volume of the capillaries in a unit of tissue increases in the latter half of the foetal period twofold in the pars distalis and fourfold in the neural lobe, due to the fact that the length of the capillaries per unit of tissue grows in the former c. 10—30 % and in the latter c. 40 % and that the diameter grows in each by about 3/4.

2) The ratio between the volumes of the capillaries of the pars distalis and the neural lobe varies in the specimens 15 : 1—6 : 1. The ratio decreases during the foetal period.

3) The capillaries of the pars intermedia and pars tuberalis resemble those of the pars distalis.

4) In a newborn infant the density of the capillary network of the neural lobe is approximately the same as in the cerebral cortex of adult man.

### Résumé

L'auteur a examiné le développement des capillaires de l'hypophyse de l'être humain pendant la dernière moitié de la période fœtale et a fait les observations suivantes.

1) Le volume des capillaires dans une unité de tissu augmente pendant la deuxième moitié de la période fœtale du double dans la pars distalis et quadruplement dans le lobe neural, ce qui est dû au fait que la longueur des capillaires par unité de tissu augmente dans la première de 10 à 30 % et dans la deuxième de 40 % et que le diamètre augmente dans les deux parties d'environ 3/4.

2) Le rapport entre les volumes des capillaires de la pars distalis et du lobe neural varie dans les proportions 15 : 1, 6 : 1. Le rapport diminue pendant la période fœtale.

3) Les capillaires de la pars intermedia et de la pars tuberalis ressemblent à ceux de la pars distalis.

4) Chez le nouveau-né, la densité du réseau capillaire du lobe neural est approximativement la même que dans l'écorce cérébrale de l'homme adulte.

### **Zusammenfassung**

Verfasser hat die Kapillarentwicklung der Hypophyse beim Menschen in der zweiten Hälfte der Fötusperiode untersucht und folgendes gefunden.

1) Das Volumen der Kapillaren in einer Gewebeseinheit wächst in dieser Zeit in pars distalis auf das Doppelte, in pars proximalis auf das Vierfache, was darauf beruht, dass die Länge der Kapillaren der Gewebeseinheit im ersten Teil um ca. 10—30 %, im zweiten um ca. 40 % zunimmt und dass der Diameter in beiden um ca. 3/4 zunimmt.

2) Das Verhältnis der Kapillarovolumen zwischen pars distalis und pars proximalis wechselt zwischen 15 : 1 und 6 : 1 und nimmt im Laufe der Fötusperiode ab.

3) Die Kapillaren des pars intermedia und pars tuberalis verhalten sich wie die des pars distalis.

4) Beim Neugeborenen ist die Dichte des Kapillarnetzes der proximalen Lobe ungefähr dieselbe wie im cortex cerebialis beim Erwachsenen.

### **Resumen**

El autor ha examinado el desarrollo de los capilares de la hipófisis del ser humano durante la última mitad del período fetal y ha hecho las observaciones siguientes:

1) El volumen de los capilares en la unidad de tejido durante la segunda mitad del período fetal se duplica en la pars distalis y se cuadruplica en el lóbulo neural, lo cual es debido a que la largura de los capilares por unidad de tejido aumenta en la primera

parte del 10 al 30 % y en la segunda al 40 % y que el diámetro aumenta en las dos partes alrededor de 3/4.

2) La relación entre los volúmenes de los capilares de la pars distalis y del lóbulo neural varía en las proporciones de 15 a 1—6 a 1. La relación disminuye durante el período fetal.

3) Los capilares de la pars intermedia y de la pars tuberalis se semejan a los de la pars distalis.

4) En el recién nacido la densidad de la red capilar del lóbulo neural es aproximadamente la misma que en la corteza cerebral del hombre adulto.

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## **Sodium and Potassium Concentration of Erythrocytes and Bromsulfalein Liver Function Test in Severe Infantile Gastroenteritis**

by

**JYRKI KAHTIO and NIILLO HALLMAN**

It is a well known fact that in severe infantile gastroenteritis there is sometimes a very great loss of fluid and minerals, involving not only extracellular but also intracellular fluid and minerals. This phenomenon was described at the beginning of this century by STEINITZ, TOBLER and JUNDELL, and later by several others. However, a few years ago DARROW was the first to take into account the intracellular potassium in addition to the extracellular minerals and to plan therapy accordingly. In the course of the disease intracellular changes, in this instance the potassium concentration, are exceedingly difficult to follow. Some indication of the changes in progress are given by the red blood cells, which have been examined in different diseases e.g. by OVERMAN, GUEST and RAPOPORT and by HALLMAN.

The bromsulfalein test (BSP-test) for examining liver function was suggested for clinical use by ROSENTHAL and WHITE in 1925, and it is still considered among the most sensitive indicators of the functional capacity of the liver. On the basis of postmortem findings of fatty metamorphosis of the liver on the one hand, and certain clinical manifestations on the other, some investigators (CZERNY, FINKELSTEIN, SCHIFF, FANCONI, MARIE et al., SCHLESINGER et al., GRÜNHOLZ, etc.) have assigned to functional disturbances of the liver a more or less dominant role in the genesis of severe gastroenteritis-"toxicosis". Different liver function tests have but seldom given positive results (SCHLESINGER et al., MARIE



et al., HALLMAN and KAHTIO). In his bromsulfalein tests KAHTIO found increased retention in several patients with gastroenteritis, although in assessing this he considers that hemodynamic factors are at least as significant as the disturbances proper in the function of the hepatic cells.

The conception that the infant organism is injured in some way during severe gastroenteritis is met with, differently formulated, in practically every study dealing with this complex of symptoms. During our investigations, on this basis, of the potassium and sodium concentrations in the erythrocytes (HALLMAN) and of BSP-retention (KAHTIO), we were to some extent obliged to study the same patients affected with severe gastroenteritis, and since on comparing results we found a surprising correlation, we feel justified in treating this matter as a separate subject.

### Methods of Determination

Variations in the sodium and potassium concentrations of both plasma and the erythrocytes in the patients in this series were followed up during the course of the disease by determinations performed with heparinised blood and a flame photometer constructed by HALLMAN and LEPPÄNEN; the margin of error was found to be 1.98 per cent for potassium and 1.66 per cent for sodium.

Variations in the bromsulfalein retention were observed by using a dosage of 5 mg/kg as a 1 % saline solution and withdrawing blood specimens 45 minutes after injection of the dye. The degree of retention was determined with the Coleman spectrophotometer on a wave length of 580. As normal values the method adopted gave retentions of 0—0.4 mg% in healthy infants of the same age.

Each patient was subjected to the foregoing determinations 1 to 15 times at different intervals, depending on the course of the disease. All other determinations were made by routine methods in use at the hospital.

### Material and Therapy

Our series comprises 28 patients with severe gastroenteritis treated at the hospital March—Oct., 1949. Of these 15 were boys

and 13 girls. The ages of the patients varied on admission from 2 weeks to 9 months. Ten of them died (35 %).

The patients were treated at the hospital according to the usual system. The fluid balance was studied by routine determinations of hemoglobin, hematocrit, plasma protein, chlorides, alkali reserve, non-protein nitrogen and glucose. In the course of the disease the blood picture, prothrombin time and plasma calcium were also studied, and, if deemed necessary, the spinal fluid as well. Bacteria cultures from liquor and blood, as well as examinations of feces for pathogenic bacteria (typhoid, paratyphoid, dysentery) gave negative results. The Wassermann test was negative without exception. In addition, all were subjected to determinations of the blood group and Rh.

Shock evident in several cases at the time of admission was as a rule immediately controlled by plasma or blood infusions, which were given regularly during treatment for anemia and hypoproteinemia.

Slight or more pronounced acidosis shown in all these cases was carefully controlled by parenteral administration of 1.3 % sodium bicarbonate or 1.87 % sodium lactate, varying from 5 to 20 ccm/kg. In addition to the foregoing, the loss of fluid was also counterbalanced by 0.9 % saline solution, generally as Hartmann's solution, as well as a 5 to 10 % glucose solution.

Depending on the clinical aspect of the disease, the patients were at first given either the whole amount of fluid parenterally, or only partly per os. After 1 to 3 days' fasting, breast-milk was tentatively administered and the doses increased daily. The purpose was to give in the initial stages of the disease a daily fluid total of 200 ccm/kg. When recovery was in progress, a diet suitable to the patient's age was administered.

In order to overcome infection, the patients were generally given, depending on their weight, 20—40000 units penicillin i.m. 2 to 4 times daily for varying periods. Several were also given 20—60000 units streptomycin twice daily per os or i.m., usually only for a few days. Some patients were likewise given sulfa drugs. In addition different vitamin preparations and in some cases liver preparations were given.

With regard to potassium therapy the series is divided into two groups, the first comprising 16 patients. Five of these were given potassium only with milk. In addition, and particularly in the initial stages, 11 patients were given 100—200 ccm Darrow's solution by mouth daily. Of these 16 patients 8 died (50 %).

The patients belonging to the second group were given, in addition to peroral dosage, infusions of Darrow's solution, in the form of a subcutaneous drop infusion, altogether about 60 ccm/kg daily. Of these 12 patients 2 died (16 %).

The average time of treatment for those patients who recovered was 46 days, without any noteworthy difference between the two groups in this series.

### Results

By classifying our patients according to the highest dye retention in BSP-tests in the course of the disease, the following table was obtained. The figures in parentheses show the number of deaths.

Table 1.

Highest BSP-Retention (mg%) in 45'-Tests.

	0—0.4	0.5—1.0	1.1—2.0	> 2.0	Total
Treated Without Parenteral Potassium Therapy . . . .	0	5 (2)	5 (3)	6 (3)	16 (8)
With Parenteral Potassium	3	6	2 (1)	1 (1)	12 (2)
	3	11 (2)	7 (4)	7 (4)	28 (10)

The table shows that patients treated without parenteral potassium had higher BSP-retention than normal at some stage of the disease. The BSP-retention of patients on potassium therapy deviated less from the normal than that of patients in the preceding group.

By grouping our patients according to the lowest potassium level in the erythrocytes observed in the course of the disease, the following table was obtained. The figures in parentheses give the number of deaths.

Table 2.

## Lowest Potassium Level in Erythrocytes (mEq/L.)

	100—90	89—80	79—70	< 69	Total
Treated Without Parenteral Potassium Therapy . . . .	4 (2)	6 (2)	4 (3)	2 (1)	16 (8)
With Parenteral Potassium	4	5	2 (1)	1 (1)	12 (2)
	8 (2)	11 (2)	6 (4)	3 (2)	28 (10)

This table shows that low potassium values were relatively common in the patients of the first group, and that the lowest values of the second group occurred in patients who died.

Finally, by grouping the patients according to the highest sodium level in the erythrocytes during the disease, the following table was obtained. The figures in parentheses represent deaths.

Table 3.

## Highest Sodium Level in Erythrocytes (mEq/L).

	< 20	21—25	26—35	> 35	Total
Treated Without Parenteral Potassium Therapy . . . .	—	2 (1)	7 (2)	7 (5)	16 (8)
With Parenteral Potassium	—	5	4	3 (2)	12 (2)
	0	7 (1)	11 (2)	10 (7)	28 (10)

It will be seen that increased sodium values in the erythrocytes occur to a relatively higher extent in the first group, corresponding to lower potassium levels. Death occurred most frequently among those patients who had the highest sodium levels. In the second group the highest sodium values are also to be found among the fatal cases.

The foregoing tables demonstrate that there is a correlation between extreme potassium and sodium values in the erythrocytes on the one hand, and the course of the disease as well as the results of treatment on the other. Those patients who had a considerably increased BSP-retention at some stage of the disease also exhibited mineral values which deviated markedly from the normal. *Fig. 1* represents the relation between dye-retention in BSP-tests and the potassium level in the erythrocytes examined simultaneously.

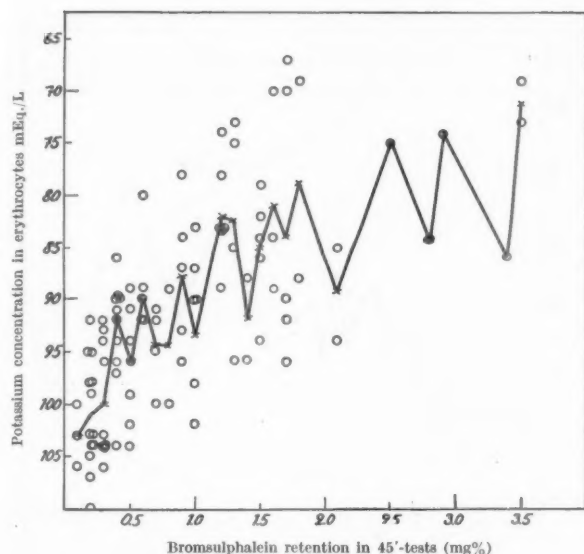


Fig. 1. Correlation of potassium concentration of erythrocytes with bromsulphalein retention in severe gastroenteritis of infants.

A total of 100 simultaneous determinations were made for different patients. It appears clear that BSP-retention being higher than normal, the potassium concentration of the red blood cells is most frequently lowered. The same applies to sodium values, (Fig. 2) except that they are — in contradistinction to potassium figures — higher than normal. Ninety five such determinations were made. There are naturally exceptions, but the correlation existing is best illustrated by observing individual patients, of whom we give some typical examples.

*Case 1*, who recovered, was a patient treated without parental potassium (Fig. 3). The curves show clearly how the potassium concentration of the erythrocytes became greatly much reduced during the disease, while the sodium concentration increased correspondingly. Simultaneously abnormal BSP-retention was manifested. The food tolerance of the patient was satisfactory,

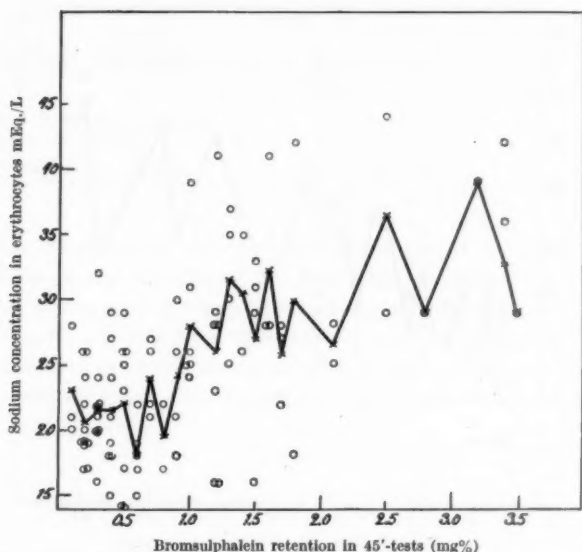


Fig. 2. Correlation of sodium concentration of erythrocytes with bromsulphalein retention in severe gastroenteritis of infants.

and with the increase of the daily amount of milk, the intracellular minerals as well as BSP-retention returned to normal. There was, however, a relapse during treatment in the course of which the weight was reduced by 300 g, but it did not seem to affect the mineral and the BSP-retention values. Similar phenomena could be observed in several patients who recovered without parenteral potassium therapy.

Cases 2, 3 and 4 were patients treated without parenteral potassium, who died within a few days of the onset of the disease (Fig. 4).

Case 2 had the same correlation between intracellular minerals and BSP-retention as the first example.

Case 3 had a low potassium concentration in the red blood cells, which as early in the beginning of treatment showed a rising tendency, as did the sodium concentration. The BSP-retention

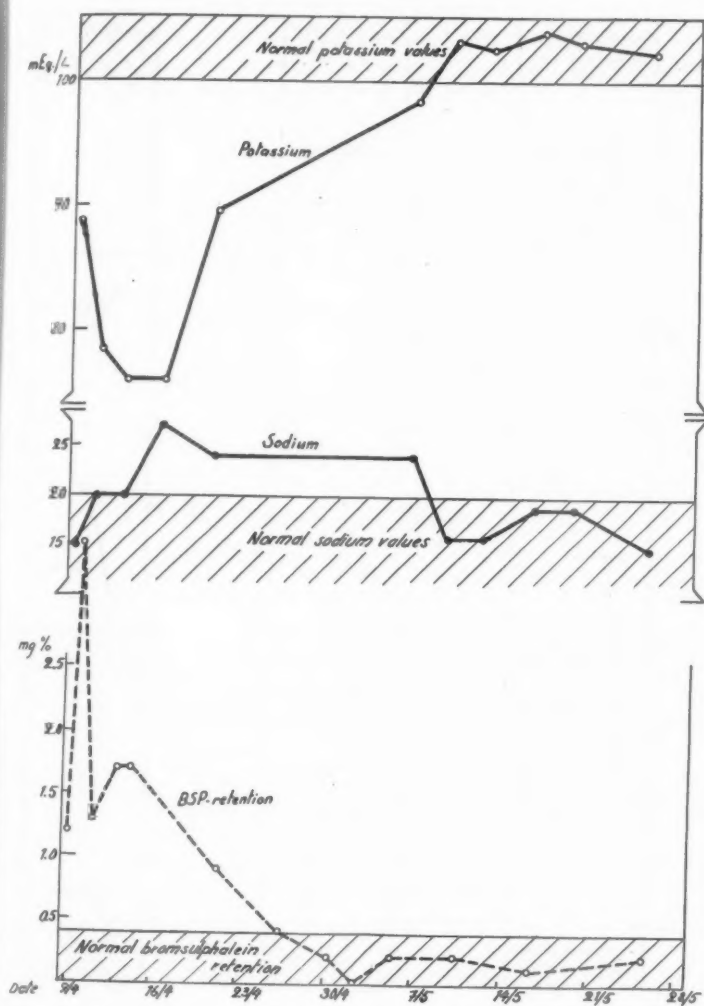


Fig. 3. Case No. 1395. Potassium and sodium concentration in erythrocytes (mEq./L.). — Bromsulphalein retention in 45'-test (mg%).

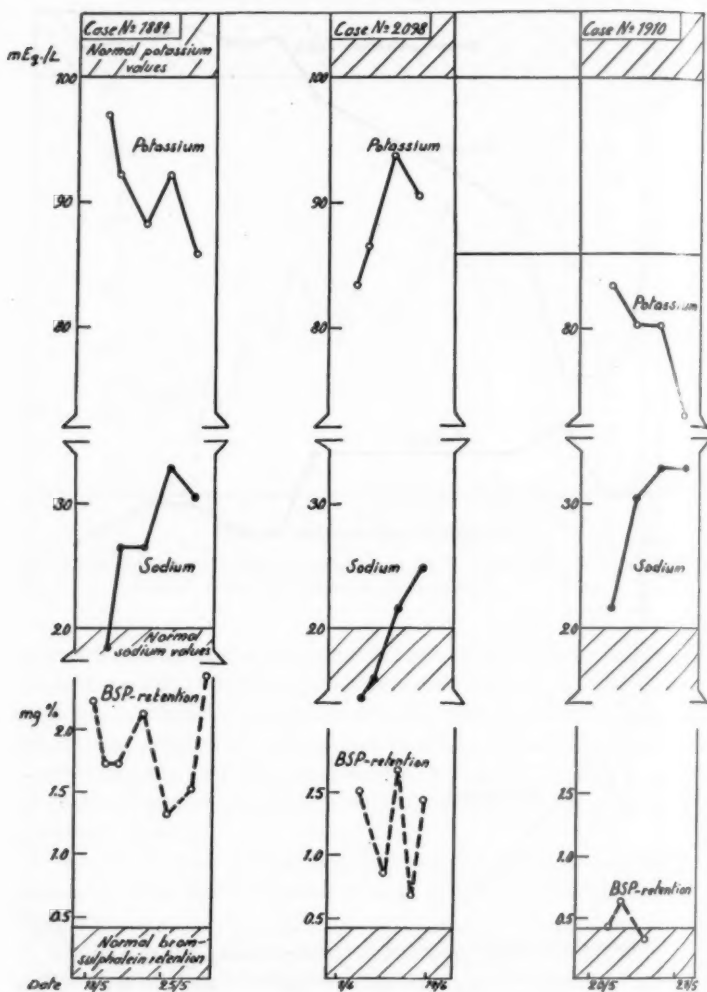


Fig. 4. Potassium and sodium concentration in erythrocytes (mEq./L). — Bromsulphalein retention in 45'-tests (mg%).



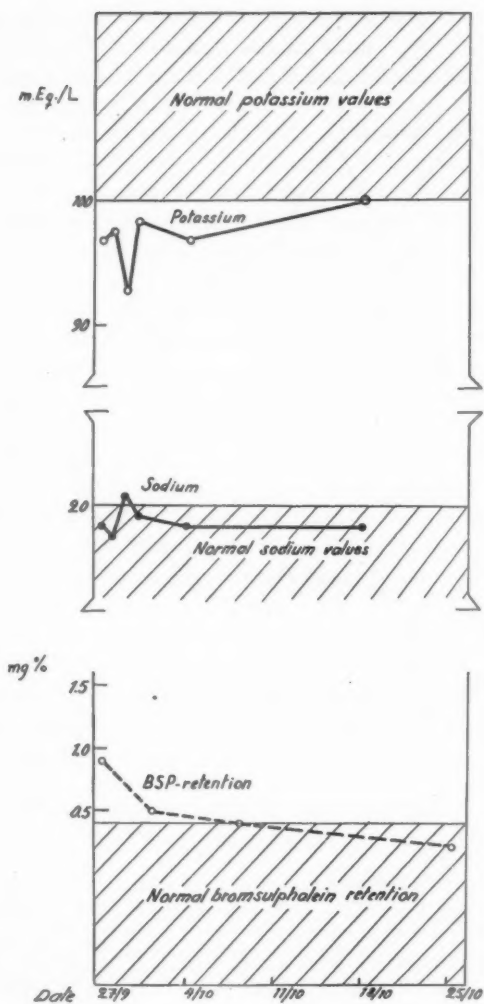


Fig. 5. Case No. 3272. Potassium and sodium concentration in erythrocytes (mEq./L.). — Bromsulphalein retention in 45'-tests (mg%).

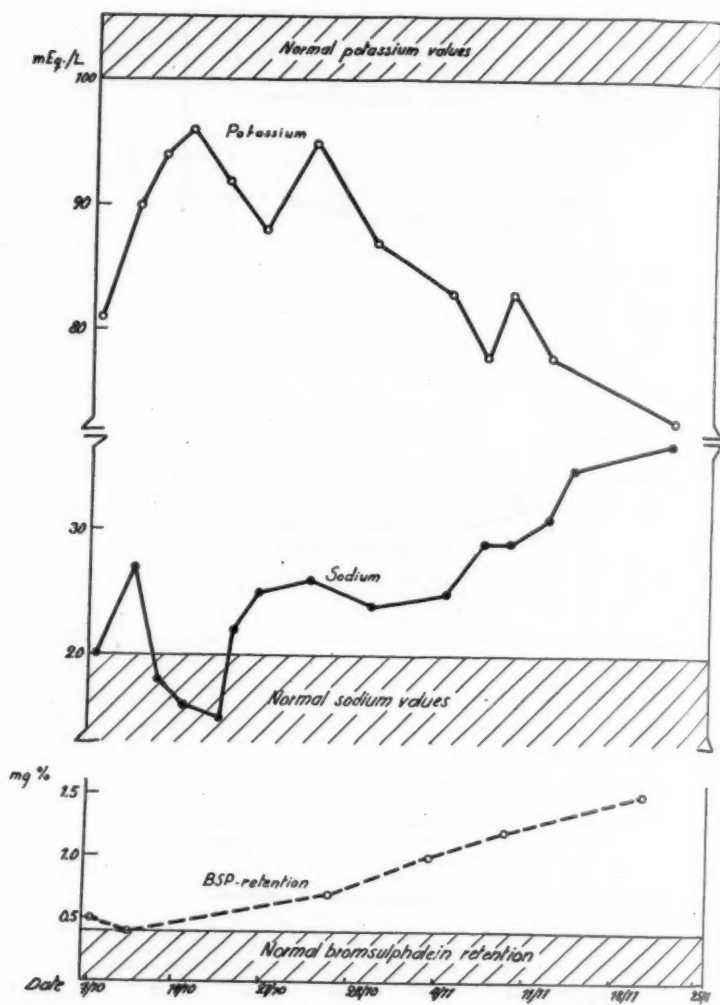


Fig. 6. Case No. 3396. Potassium and sodium concentration in erythrocytes (mEq./L.). — Bromsulphalein retention in 45'-tests (mg%).

remained on an abnormal level the whole time. Some recoveries exhibited similar changes.

*Case 4* also had a low intracellular potassium concentration at the beginning of treatment, but it fell still more while treatment was in progress simultaneously with a marked rise in the sodium concentration. BSP-retention differed little from the normal. In all the cases treated without parenteral potassium the loss of intracellular potassium was reflected more or less clearly in the reduced values of the plasma potassium. Simultaneously there were often increased plasma sodium values.

*Case 5* was a typical example of a patient treated with parenteral potassium who recovered (*Fig. 5*). The changes shown in the intracellular minerals were less pronounced, and the BSP-retention deviated from the normal only at the beginning of treatment. The plasma potassium remained normal all the time, while the plasma sodium showed slight variations.

*Case 6* was the second in which death occurred in a patient treated with parenteral potassium (*Fig. 6*). On admission the BSP-retention was only slightly increased. The potassium concentration in the erythrocytes was low but returned to normal in the course of a few days. When treatment had been in progress for about two weeks, the intracellular potassium began to fall steadily, the intracellular sodium exhibiting a corresponding rise. Simultaneously there was an increase in the BSP-retention which continued while the disease ran its course. The plasma potassium also showed a pronounced tendency to fall. The observations were identical in the second fatal case.

### Case Reports

**Case 1.** No. 1395/49, boy aged 2 mo. Diagnosis *Gastroenteritis ac. Intoxicatio*. Weight at birth was 3 650 g. Became ill April 3, 1949, with vomiting and diarrhea.

On admission to hospital April 9 he was tired, distressed, greyish and dehydrated. His eyes were hollow and staring; he reacted slowly when pinched. Weight 4 050 g. Temperature 38° C. Heart and lungs: nothing abnormal. The feces were loose, mucous, greenish and offensive. He vomited a little. Hb. 95/111, R.B.C. 5.52 million, Hematocrit 50, Proteins 6.5 g%, Alkali Reserve 9.9 mEq/L, Non-Protein Nitrogen 41 mg%,

W.B.C. 10 800, Plasma Na. 141 mEq/L, K. 2.8 mEq/L, R.B.C. Na. 15 mEq/L, K. 86 mEq/L, BSP-retention 1.2 mg%.

April 10 weight 4 300 g. Diarrhea and vomiting continued. Still listless. Alk.R. 20.2 mEq/L. BSP-retention 3.5 mg%.

April 11 weight 4 150 g. The feces were as before. Hb. 73/85, R.B.C. 3.60 mill., Hcr. 43, Prot. 5.8 g%, Alk.R 21.1 mEq/L, Non-Prot. N. 18 mg%. Plasma Na. 147 mEq/L, K. 3.3 mEq/L, R.B.C. Na. 20 mEq/L. BSP-retention 1.3 mg%.

April 13 weight 3 900. Diarrhea was less severe. R.B.C. Na. 20 mEq/L, K. 70 mEq/L, BSP-retention 1.7 mg%.

April 16 weighed 4 050 g. He was brighter and ate fairly well. Feverish, lungs, nil. Alk.R. 26.1 mEq/L.

April 19 weight 4 100 g. No diarrhea. He was moderately lively.

April 29 weighed 4 300 g. Ate fairly well and was much better. BSP-retention had returned to normal.

May 6 weight 4 150 g. The feces became loose again. He was more listless and his appetite was poor. Alk. R. 16.2 mEq/L. Plasma Na. 155 mEq/L, K. 53 mEq/L, R.B.C. Na. 24 mEq/L, K. 98 mEq/L. BSP-retention 0.2 mg%.

May 16 weighed 4 150 g. Was fairly alert, ate well, but there was no gain in weight. R.B.C. Na. 19 mEq/L, K. 105 mEq/L. BSP-retention 0.1 mg%.

May 30 weighed 4 400 g. He was happy and active. Was discharged as convalescent.

**Case 2.** No. 1884/49, boy aged 4 mo. Diagnosis *Gastroenteritis ac. Intoxicatio*. Weight at birth 3 300 g. The onset of the disease occurred on May 10, 1949, with vomiting and diarrhea. The weight fell by 500 g.

On admission May 18 looked extremely ill, listless, grey and dehydrated. The weight was 5 050 g, temperature 37.7° and he had a cough. Heart and lungs were normal. The abdomen was distended. Diarrhea + +, watery, green and offensive. He vomited excessively and the vomit was streaked with blood. Prothrombin time was 72/22 sec.

May 19 the weight was 5 200 g. The general condition was unchanged. Hb. 70/71, R.B.C. 4.300 mill., Hcr 39, Prot. 6.1 g%, Alk. R 16.2 mEq/L. Non-Prot. N 36 mg%, W.B.C. 13 800. BSP-retention 2.2 mg%.

May 20 he weighed 5 300 g. Temperature was 39.5°. Cough, lungs-. Alk. R 22 mEq/L. Plasma Na. 141 mEq/L, K. 31 mEq/L, R.B.C. Na. 18 mEq/L, K. 96 mEq/L. BSP-retention 1.7 mg%.

May 23 weight 4 950 g. He continued to vomit a great deal. Small twitchings were noticeable in eyes and hands. Blood Ca 7.7 mg%. Alk. R 31.5 mEq/L. Plasma Na. 144 mEq/L, K. 3.5 mEq/L. RBC. Na. 28 mEq/L, K. 85 mEq/L.

May 25 weight down to 4 800. Vomiting continued, but the convulsions had ceased. Hb. 57/66, R.B.C. 3.64 mill., Hcr. 28, Prot. 6.6 g%, Alk.

R 34.2 mEq/L, Non-Prot. N 33 mg%. R.B.C. Na. 36 mEq/L, K. 90 mEq/L BSP-retention 1.3 mg%.

May 29 weighed 5 000 g. The general condition became progressively worse, BSP-retention was 2.4 mg%. Death occurred.

*Autopsy No. 175/49:* Gastroenteritis catarrhalis. Oedema pulmonum. Metamorphosis adiposa hepatis. Degeneratio parenchymatosa renum.

**Case 3.** No. 2098/49, boy aged 6 m. Diagnosis *Gastroenteritis ac. Intoxicatio*. His birth weight 2 000 g. He became ill on May 24 with slight diarrhea, and vomited now and then. The loss in weight was 700 g.

On admission June 7 he appeared seriously ill, dehydrated and grey. There were abundant petechia in the abdominal wall. The prothrombin time was 30/22 sec. The weight was 4 450 g, temperature 37°. Heart and lungs -. Alk.R 7.2 mEq/L.

June 8 general condition continued poor. Profuse green stools contained blood. Hb. 77/89, R.B.C. 5.1 mill., Hcr. 45, Prot. 5.2 g%, Alk.R 9.9 mEq/L. Non-Prot.N 179 mg%, W.B.C. 20 200. Plasma Na. 121 mEq/L, K. 4.0 mEq/L. R.B.C. Na. 13 mEq/L, K.79 mEq/L. BSP-retention 1.5 mg%.

June 10 weight 4 700 g and the general condition had improved. Alk.R 25.2 mEq/L. BSP-retention 0.8 mg%.

June 13 weight 4 500 g. The diarrhea had ceased. Alk.R 23.4 mEq/L. Plasma Na. 139 mEq/L, K. 2.4 mEq/L. R.B.C. Na. 26 mEq/L, K. 88 mEq/L. BSP-retention 1.4 mg%. Prothrombin time 32/22 seconds, in spite of daily vitamin K injections. Blood Ca 8.0 mg%.

June 14 temperature rose to 40°; he had severe convulsions. Death followed.

*Autopsy No. 194/49:* Gastroenteritis catarrhalis. Oedema pulmonum. Metamorphosis adiposa hepatis.

**Case 4.** No. 1910/49, girl aged 3 mos. 2 wks. Diagnosis *Gastroenteritis subacuta*. Birth weight 3 140 g. Onset May 7, with vomiting and diarrhea. The weight decreased 1 100 g. She was treated at another hospital. On admission May 20 her general condition was poor, she was thin and pale, and her eyes were sunken. Her stools were watery and the vomit contained blood.

May 21 weight 3 950 g, temperature 38°. Heart and lungs -. Hb. 76/88, R.B.C. 4.22 mill., Hcr. 43, Prot. 5.9 g%. Alk.R 15.3 mEq/L, Non-Prot.N 41 mg%, W.B.C. 21 400. Plasma Na. 126 mEq/L, K. 1.8 mEq/L. R.B.C. Na. 22 mEq/L, K. 79 mEq/L. BSP-retention 0.4 mg%.

May 23 weight 3 850. The diarrhea had improved, but she continued to vomit. Alk.R 25.2 mEq/L. Plasma Na. 151 mEq/L, K. 1.6 mEq/L. R.B.C. Na. mEq/L, K. 75 mEq/L. Twitchings occurred in eyes and hands. The Blood Ca was 6.3 mg%.

May 25 she weighed 3 950 g. Alk.R 24.7 mEq/L, Plasma Na. 162 mEq/L, K. 1.8 mEq/L, R.B.C. Na. 36 mEq/L, K. 75 mEq/L. BSP-retention 0.3 mg%.

May 27 weighed 4 050 g and was listless. Alk.R 34.2 mEq/L, R.B.C. Na. 36 mEq/L, K. 66 mEq/L. Death occurred.

*Autopsy No. 171/49: Gastroenteritis catarrhalis. Oedema pulmonum. Metamorphosis adiposa hepatis.*

**Case 5.** No. 3272/49, boy aged 6 wks. Diagnosis *Gastroenteritis ac. Intoxicatio*. Weight at birth 2 860 g. He fell ill on Sept. 25 with vomiting and diarrhea.

On admission Sept. 27 he looked acutely ill, grey and dehydrated. He did not react when pinched. His weight was 3 000 g, temperature 37.2°. Heart and lungs were normal. His stools were loose, green and offensive. He vomited. Hb. 78/90, R.B.C. 4.12 mill., Alk.R 5.8 mEq/L, W.B.C. 11 200, Plasma Na. 140 mEq/L, K. 4.8 mEq/L, R.B.C. Na. 18 mEq/L, K. 96 mEq/L, BSP-retention 0.9 mg%,

Sept. 29 weight 3 400 g. He was unmistakably brighter, but feces were still very loose. Alk.R 24.3 mEq/L, R.B.C. Na. 21 mEq/L, K. 91 mEq/L.

Oct. 4 weight 3 050 g. He was tired and vomited, but ate fairly well.

Oct. 11 weighed 3 400 g. The bowels were functioning normally, the appetite was good, and the baby active. BSP-retention had returned to normal.

Oct. 18 weighed 3 700 g, was alert and happy, ate well.

Oct. 25 weight 3 800 g. The patient had made a good recovery and was discharged.

**Case 6.** No. 3396/49, girl aged 2 mos. and 2 wks. Diagnosis *Gastroenteritis ac. Intoxicatio*. She fell ill on Oct. 1 with vomiting and diarrhea. The weight loss was 1 500 g (?). On admission Oct. 7 she was distressed, greyish and dehydrated. Her weight was 3 800 g, temperature 38°. Heart and lungs, n.a.d. The stools were mucous, green and watery. Hb. 66/77, R.B.C. 3.34 mill., Her. 34, Prot. 5.8 g%, Alk. R 18.9 mEq/L, Non-Prot.N 17 mg%, W.B.C. 19 800. Plasma Na. 143 mEq/L, K. 5.6 mEq/L, R.B.C. Na. 20 mEq/L, K. 81 mEq/L. BSP-retention 0.5 mg%.

Oct. 10 weight 4 100 g. She was still tired. Alk.R 23.4 mEq/L, R.B.C. Na. 27 mEq/L, K. 90 mEq/L. BSP-retention 0.4 mg%.

Oct. 14 weight 4 300 g. She was less tired. Diarrhea continued and she vomited profusely.

Oct. 19 weighed 3 800. Diarrhea had increased in severity; the stools contained blood. Alk.R 15.3 mEq/L.

Oct. 22 weight 4 100 g. General condition improved.

Oct. 30 weight 4 000 g. She was tired, pale, listless. Ate poorly and vomited more. Hb. 79/91, R.B.C. 3.99 mill., Her. 40, Prot. 6.9 g%, Alk.R 23.4 mEq/L, Non-Prot. N 32 mg%, Plasma Na. 143 mEq/L, K. 4.8 mEq/L, R.B.C. Na. 24 mEq/L, K. 87 mEq/L.

Nov. 7 weighed 3 700 g. General condition continued poor. The feces were loose and mucous and she vomited. Alk.R 10.3 mEq/L,

R.B.C. Na. 29 mEq/L, K. 78 mEq/L. The BSP-retention was increased.

Nov. 14 weight 3 500 g. The baby was unconscious and pale. Respirations stertorous and Cheyne-Stokes. She was fed through a tube. Alk.R 20.7 mEq/L.

Nov. 21 weight 3 450 g. She was deeply unconscious, but respiration was improved. Hb. 77/89, R.B.C. 4.32 mill., Her. 36, Prot. 4.9 g%, Alk.R 13 mEq/L, Non-Prot.N 51 mg%, Plasma Na. 148 mEq/L, K. 2.3 mEq/L, R.B.C. Na. 37 mEq/L, K. 73 mEq/L. BSP-retention 1.4 mg%.

Nov. 24 weight 3 250 g. The patient died.

*Autopsy No. 327/49:* Hyperemia leptomeningeum. Atrophia. Oedema pulmonum. Metamorphosis adiposa hepatis. Nephrosis.

### Discussion

As mentioned initially, several investigators consider that the cells of the organism become severely damaged in the course of acute gastroenteritis. Therefore, they claim, recovery is exceedingly slow, and death sometimes ensues even if the fluid and mineral balance can be controlled and maintained on a normal level, at least as far as the plasma, which is easily examined, is concerned.

Yet it is difficult to demonstrate the damage undergone by the cells. Balance tests and tissue analyses performed by DARROW reveal that during the disease the organism also loses its intracellular minerals, in the first instance potassium. However, owing to persistent vomiting it is difficult to make balance tests in those cases which are most severe, and in tissue analyses one has had to be satisfied so far with calculations based on certain premises, as in the case of Darrow, who assumed that chloride always remains outside the cells.

Our series shows marked alterations in the potassium and sodium levels of the erythrocytes. It is hazardous to maintain, solely on this basis, that similar changes occur also in other body cells. It is known in fact that chloride increases in the erythrocytes during acidosis (VAN SLYKE, LÉVY, RIBADEAU-DUMAS, GERBRASI), even if as KERPEL-FRONIUS claims on the basis of balance tests this does not occur elsewhere in the organism. Where potassium and sodium are concerned, earlier investigators have been able, in

performing balance tests during the disease, to establish changes similar to those now found by us in the erythrocytes. It is difficult to conceive that such extensive changes in cellular minerals could fail to affect the function of the cells.

As already mentioned at the beginning, some investigators have advanced theories according to which disturbances in the liver function occupy a more or less central position in the genesis of severe gastroenteritis, yet such patients have but seldom been subjected to so-called liver function tests. Among these most results have been attained with bromsulfalein, but in many cases the main cause of increased bromsulfalein retention is probably hemodynamic disorders characteristic of the disease (KAHTIO). Yet it appears evident that at least in some individual cases, there are also other factors, above all the dysfunction of hepatic cells, which exercise a similar effect.

If we postulate that the changes observed by us in erythrocytes also occur in hepatic as well as all other cells, it appears not inconceivable that their function is also affected by these changes as such.

Changes in cellular minerals are no primary phenomena. They are preceded by dehydration of the organism and changes in the extracellular fluid. It is a different matter whether dehydration as such produces damage to cells and loss of potassium, whether this is brought about by the infection itself or an accumulation in the tissues of toxic substances due to it, or whether the effect is possibly transmitted by the autonomic nervous system.

### Summary

1. A study of the potassium and sodium concentrations in the erythrocytes in 28 infants suffering from severe gastroenteritis is presented. Simultaneously determinations of bromsulfalein retention were made and the results compared.

2. In the majority of cases during the acute stage of the disease the potassium of the erythrocytes decreased and the sodium increased, these changes were controlled while recovery was in progress.



3. A higher bromsulfalein retention than normal was also demonstrated during the disease in the majority of the cases.

4. Practically always a clear correlation could be established between these phenomena.

### Résumé

1. On présente une étude sur les concentrations de potassium et de sodium dans les érythrocytes de 28 enfants souffrant de gastroentérite grave. Simultanément on a établi des déterminations de la rétention bromsulfaléine et les résultats ont été comparés.

2. Dans la majorité des cas, pendant la période aiguë de la maladie, le potassium des érythrocytes a augmenté et le sodium a diminué; ces changements ont été contrôlés au cours de la guérison.

3. Une rétention bromsulfaléine plus élevée que la normale a aussi été démontrée pendant la maladie dans la majorité des cas.

4. On a pratiquement toujours pu établir une corrélation évidente entre ces deux phénomènes.

### Zusammenfassung

1. Die Arbeit enthält eine Studie der Kalium- und Natrium-Konzentration der Erythrozyten in 28 Fällen von schwerer Gastroenteritis. Die Resultate werden mit gleichzeitigen Bromsulfalein-Bestimmungen verglichen.

2. In der akuten Phase der Krankheit war meistens der Kalium-Wert gesenkt, der Natrium-Wert gesteigert; diese Veränderungen wurden bei fortschreitender Genesung kontrolliert.

3. Die Bromsulfalein-Retention war gleichfalls meistens gesteigert.

4. So gut wie regelmässig wurde eine offenbare Korrelation zwischen diesen Veränderungen nachgewiesen.

### Resumen

1. Se presenta un estudio sobre las concentraciones de potasio y de sodio en los eritrocitos de 28 niños que podían de gastro-

enteritis aguda. Simultáneamente se han hecho determinaciones de la retención de bromsulfaleína y los resultados han sido comparados.

2. En la mayoría de los casos, durante el período agudo de la enfermedad, el potasio de los eritrocitos ha aumentado y el sodio ha disminuido; estos cambios han sido comprobados en el curso de la curación.

3. Durante la enfermedad ha sido demostrada también en la mayoría de los casos una retención de bromsulfaleína más elevada que la normal.

4. Casi siempre se ha podido establecer una correlación evidente entre estos dos fenómenos.

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## **Thiocyanate Space of Body and Mineral Concentration of Erythrocytes in Severe Infantile Gastroenteritis**

by

**NIILO HALLMAN and JYRKI KAHTIO**

One of the most characteristic features in severe infantile gastroenteritis is the loss of fluid and minerals by the organism. This occurs both in the extracellular fluid and in the cells themselves, as demonstrated by numerous workers in the course of several years. It is typical of the course of the disease, particularly in severe cases, that acute stage is followed by a longer or shorter period during which weight is not gained at the usual rate and some other disorders can be observed as well.

ROBINOW and HAMILTON (1940), as well as KERPEL-FRONIUS and KOVACH (1948), have demonstrated in their determinations of the extracellular fluid by the thiocyanate method that the relative amount of this fluid is increased in chronic infantile malnutrition. Post-diarrheal states of severe gastroenteritis resemble in many respects those already mentioned. It has been our intention to study the changes associated with severe gastroenteritis by applying the thiocyanate method used in several investigations to determine the extracellular fluid (CRANDALL and ANDERSON, etc.). Since the distribution of fluids in the organism depends largely on the minerals, we have made simultaneous observations of mineral concentrations in plasma and erythrocytes in the patients belonging to our series.

### **Methods of research**

For determinations of the TCS (thiocyanate space) we used a 1  $\frac{1}{2}$  % NaSCN solution administered to the patient as an infusion into the scalp veins; the dose was 1 ccm per kg body weight, i. e. 45—120 mg NaSCN at

a time, the patient having previously been starved for 6 to 8 hours. The blood specimens were withdrawn after 1 to 2 hours from the superior sagittal sinus carefully avoiding hemolysis. The plasma proteins were precipitated with 20 % trichloroacetic acid and 1 ccm clear, filtered supernatant fluid was used for determinations, diluted with distilled water to 1:15. The determinations were performed with the photoelectric colorimeter of Leitz (filter C), and the above-mentioned solution was used to adjust the colorimeter. The color was developed by adding 1 ccm of 5 % ferric nitrate reagent (CRANDALL and ANDERSON) and the galvanometer read immediately afterwards. All determinations were duplicate and their results showed divergencies of  $\pm 3$  %. The thiocyanate concentration was obtained by comparisons of results with the NaSCN solution of known concentration.

The thiocyanate space was calculated by the simple formula  $TCS = a/c$ ,  $a$  being the injected quantity of NaSCN (mg) and  $c$  the concentration in the plasma filtrate (mg %). The absolute quantity was calculated in addition in per cent of the body weight. Furthermore, the body weight of the patients was compared to a theoretical ideal weight, obtained in the usual way by adding 600 g per month to the weight at birth.

The first determination of TCS in patients suffering from gastroenteritis was generally made at the same time as the first infusion and the second after dehydration was cleared up clinically. Thereafter determinations were performed once a week, varying from 5 to 10 times per patient. Prior to injecting fresh dye, the thiocyanate concentration in serum was determined regularly and taken into account in calculating the TCS.

The sodium and potassium determinations were performed with a flame photometer (HALLMAN and LEPPÄNEN) and all other examinations by the routine laboratory methods used at the hospital.

### Material

Our series comprises 27 infants and 3 adults. Of the babies 14 were affected with severe gastroenteritis, and in 11 of them the variations of TCS could be systematically observed from the beginning of treatment until discharge from hospital. The controls consisted of 8 normal children (4 boys and 4 girls) aged from 1 to 10 months and 5 infants who were clearly underweight (2 boys and 3 girls) aged from 3 to 18 months. The ages of the gastroenteritis patients varied from 3 weeks to 7 months. Five of them were girls and 9 boys, 2 of them fatal issues (No. 2896/49 and 2986/49).

The fluid therapy of gastroenteritis patients was administered according to the scheme developed at the hospital, largely based on the lines drawn up by DARROW. To overcome infection, antibiotics were given when necessary, and therapy generally planned for each case.

### Present Investigation

Table 1 illustrates the weight variations of our gastroenteritis patients and changes in the TCS, as well as in the blood chemistry. On admission, the patients were all severely dehydrated and acidosed. In 4 babies the alkali reserve was below 10 mEq/L, in 7 10–15 mEq/L and in 3 15–20 mEq/L. In the course of the first few days dehydration was cleared up and acidosis controlled. In 1 case only (No. 2663/49) the alkali reserve rose temporarily in the stage of recovery to levels which must be considered above the normal. In spite of the hemoconcentration as illustrated by hemoglobin, the plasma protein was generally low from the beginning, which is consistent with the results already obtained in Finnish series (PALMBERG). It was not possible to establish any clear correlation between the results of the above-mentioned investigations and the TCS values.

It has been demonstrated (GUEST, HALLMAN) that the potassium concentration in the erythrocytes is often low in severe dehydration. Of the 11 cases followed up by us, this was found in 7 patients. In spite of the potassium therapy instituted, the potassium concentration of the red blood corpuscles continued to fall in 3, as it also did in all those patients in whom it had been normal on admission. The lower potassium level was as a rule balanced in the erythrocytes by an increased sodium concentration which returned to normal simultaneously with the potassium values or soon afterwards.

The main interest is due to variations in the TCS. In order to test the method, some determinations were performed on normal adults (Table 2). In 3 cases the specimens were taken after 60 and 120 minutes.

The results are consistent with figures obtained in earlier investigations (LAVIETES et al.) and reveal in addition that a withdrawal of samples at an interval of 1 to 2 hours after injection of the dye is of no particular significance, even if the amounts excreted into the urine are disregarded.

The TCS values obtained by us for normal infants are also consistent with those of earlier investigators (FLEXNER et al.,

Table 1

No.	Age, months	Sex	Date	Weight		Thiocyanate space		Blood			Plasma					Erythr.	
				gms	as % of ideal weight	gms	as % of body weight	Hgb.	Erythr. mill./cmm	Hcr.	Prot. g%	Cl' mEq./L	HCO <sub>3</sub> ' mEq./L	K' mEq./L	Na' mEq./L	K' mEq./L	Na' mEq./L
Case 1 2704/49	2	♀	9/8	4.300	87	1.550	36	91/105	4.51	44	6.3	101	8	4.6	143	101	18
			10/8	4.450	92	—	—	—	—	—	5.3	97	20	5.8	139	91	21
			12/8	4.600	93	2.540	55	—	—	—	5.4	97	22	3.2	153	100	25
			18/8	4.500	89	1.920	43	—	—	—	5.2	115	26	7.0	163	122	20
			22/8	4.350	84	2.140	49	—	—	—	—	—	—	7.5	152	105	17
			30/8	4.350	82	1.750	40	—	—	—	—	—	—	—	141	100	20
			7/9	4.850	90	1.750	36	92/106	5.26	—	—	—	—	—	—	—	—
Case 2 2730/49	3	♀	10/8	5.000	91	1.790	36	—	—	—	—	—	—	—	—	—	—
			12/8	4.200	89	1.630	39	74/86	4.29	44	5.5	101	18	5.0	126	101	20
			12/8	4.100	88	—	—	65/75	3.68	34	5.5	101	23	5.7	149	86	37
			12/8	4.200	84	2.630	62	45/53	2.61	20	5.4	107	29	4.3	143	84	32
			15/8	4.300	85	1.970	46	—	—	—	5.4	101	28	4.2	140	104	23
			22/8	4.250	84	2.270	53	—	—	—	6.3	115	22	4.2	145	107	20
			30/8	4.000	78	1.510	38	—	—	—	—	—	—	—	—	—	—
Case 3 2753/49	1	♀	7/9	4.100	77	1.440	35	—	—	—	—	—	—	—	—	—	—
			19/9	4.350	80	1.440	33	92/113	5.35	—	—	—	—	—	—	—	—
			5/10	4.650	80	1.500	32	69/80	4.03	—	—	—	—	—	—	—	—
			12/8	3.350	86	1.240	37	—	—	—	5.7	107	7	6.4	138	95	20
			14/8	3.450	86	—	—	—	—	—	—	—	13	4.2	148	84	30
			15/8	3.500	87	1.670	48	79/91	3.51	35	4.8	107	19	3.0	147	100	33
			18/8	3.550	86	1.720	48	—	—	—	5.5	94	26	5.0	144	102	27
Case 4 2778/49	2	♂	24/8	3.350	80	2.000	60	—	—	—	—	24	—	—	99	27	
			22/8	3.350	77	1.340	40	—	—	—	4.8	107	22	—	144	100	20
			9/9	3.750	82	1.500	40	83/96	3.91	—	—	—	—	—	—	—	—
			16/8	3.000	70	1.290	43	88/102	3.99	43	5.5	77	12	6.4	—	105	—
			18/8	3.350	78	—	—	79/91	3.75	—	5.6	82	22	5.7	126	96	18
			19/8	3.250	76	—	—	—	—	—	5.5	97	26	5.3	141	83	22
			21/8	3.200	73	1.630	51	—	—	—	5.5	95	23	6.2	149	95	23
Case 9 2896/49	3	♂	24/8	3.250	73	2.020	62	—	—	—	5.5	94	24	5.0	144	99	21
			31/8	3.250	70	1.540	48	—	—	—	—	—	—	—	146	105	23
			19/9	3.550	74	1.430	40	75/87	4.17	—	—	—	—	—	—	—	—
			28/9	3.750	73	1.500	40	—	—	—	—	—	—	—	—	—	—
			15/10	4.050	74	1.340	33	76/88	3.90	—	—	—	—	—	—	—	—
			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

No.	Age, months	Sex	Date	Weight		Thiocya- nate space		Blood			Plasma					Erythr.	
				gms	as % of ideal weight	gms	as % of body weight	Hgb.	Erythr. mill./cmm	Hcr.	Prot. g%	Cl' mEq./L	HCO <sub>3</sub> ' mEq./L	K' mEq./L	Na' mEq./L	K' mEq./L	Na' mEq./L
Case 5 2787/49	6	♂	17/8	7.900	105	2.040	26	70/81	4.22	34	6.9	101	14	4.6	138	107	19
			18/8	8.100	107	—	—	—	—	—	6.2	101	21	5.0	140	83	23
			21/8	8.400	110	3.250	39	—	—	—	6.3	107	28	7.4	148	98	23
			24/8	8.300	106	3.150	38	—	—	—	—	—	—	—	—	—	—
			31/8	7.800	100	2.550	33	—	—	—	6.2	97	18	—	147	103	20
Case 6 2803/49	7	♂	7/9	8.000	99	2.300	29	65/75	4.07	—	—	—	—	—	—	—	—
			18/8	2.400	71	1.410	59	122/142	5.76	62	6.9	101	8	3.1	135	98	17
			19/8	2.700	79	—	—	—	—	—	7.7	107	11	—	—	86	15
			20/8	2.400	71	—	—	—	—	—	—	—	—	16	5.8	131	92
			23/8	2.550	73	1.610	63	—	—	—	—	—	—	27	5.0	140	94
	2	♂	31/8	2.500	70	1.050	42	—	—	—	—	—	—	—	—	—	—
			9/9	2.400	62	1.550	65	> 140	6.43	—	—	—	—	—	—	—	—
			19/9	2.750	67	1.220	44	—	—	—	—	—	—	—	—	—	—
			26/9	2.950	70	1.220	41	90/104	5.26	—	—	—	—	—	—	—	—
			23/10	2.950	63	9.180	40	80/93	4.60	—	—	—	—	—	—	—	—
Case 7 2846/49	1 1/2	♂	21/8	2.900	73	1.130	40	124/144	5.22	—	7.1	121	7	8.4	151	87	22
			24/8	3.050	75	—	—	—	—	—	—	—	26	—	131	99	—
	1	♂	16/9	2.950	64	1.220	41	107/124	5.22	—	—	—	—	—	—	92	28
			19/9	3.150	66	1.340	42	—	—	—	—	—	—	—	—	—	—
			1/10	3.750	74	1.540	41	—	—	—	—	—	—	—	—	—	—
Case 8 2863/49	2	♂	24/8	2.950	67	1.500	51	107/124	5.22	49	5.4	97	13	3.2	128	64	25
			26/8	3.100	69	—	—	—	—	—	4.9	87	15	2.0	133	69	25
			30/8	2.850	63	1.560	55	—	—	—	5.4	97	18	5.0	141	80	28
			7/9	3.250	69	1.620	50	90/104	4.88	—	4.7	90	37	5.2	133	79	34
	3	♂	17/9	3.350	68	1.500	45	78/90	3.85	—	6.2	100	27	5.5	156	97	34
			24/9	3.450	69	1.580	46	—	—	—	6.0	97	29	5.5	147	104	23
			25/10	4.200	74	1.760	42	61/71	3.11	34	4.9	97	22	—	—	—	—
			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Case 9 2896/49	6	♂	27/8	6.500	96	2.100	32	—	—	—	—	—	13	5.8	119	85	18
			30/8	6.800	100	3.050	45	92/106	6.21	54	6.2	83	22	6.2	139	95	16
			7/9	6.650	97	2.850	43	60/70	3.80	—	5.0	94	28	6.3	138	99	25
			17/9	6.500	93	2.700	42	62/72	4.01	—	—	—	24	5.4	140	110	22
	7	♂	23/9	6.000	80	2.370	40	84/97	4.85	—	—	—	27	—	134	101	29

No.	Age, months	Sex	Date	Weight		Thiocyanate space		Blood			Plasma				Erythr.	
				gms	as % of ideal weight	gms	as % of body weight	Hgb.	Erythr. mill./cmm	Hct.	Prot. g%	Cl' mEq./L	HCO <sub>3</sub> ' mEq./L	K' mEq./L	Na' mEq./L	Na' mEq./L
Case 10 2983/49	1	♂	5/9	3.800	100	1.500	40	48/56	2.44	25	6.4	103	12	7.8	141	88
			8/9	4.100	104	2.150	52	—	—	—	5.1	108	26	6.2	150	91
			17/9	3.950	100	1.670	42	62/72	3.23	—	6.1	110	23	7.9	146	105
	2		1/10	4.250	99	1.530	36	67/78	3.68	—	—	—	—	—	—	—
Case 11 2986/49	3	♂	5/9	3.800	73	1.430	38	67/78	5.22	43	5.6	94	16	—	—	—
Case 12 3058/49	4	♂	10/9	6.000	95	1.320	22	—	—	—	4.1	97	18	4.9	134	89
			17/9	5.950	94	2.150	36	71/81	4.58	—	5.0	90	20	7.4	142	98
			28/9	6.000	95	2.250	38	—	—	—	5.3	101	20	6.4	154	107
			1/10	6.100	92	1.960	32	—	—	—	—	—	—	—	—	—
Case 13 2563/49	1	♀	26/7	2.250	68	1.250	56	73/85	3.67	—	4.9	115	15	—	—	—
Case 14 2446/49	1	♂	14/7	4.150	87	1.310	32	67/78	3.76	36	5.3	106	14	—	—	—
			28/7	4.450	88	1.950	44	62/72	3.80	—	—	—	—	—	—	—

FELLERS et al., KERPEL-FRONIUS and KOVACH), being on a relatively higher level than those of an adult (Fig. 1). Some determinations performed by us on underweight infants (Fig. 1) demonstrated that they had a higher TCS compared to their weight than normal babies, as shown formerly (ROBINOW and HAMILTON, KERPEL-FRONIUS and KOVACH). The average weight of normal infants in our material was 97 % of the theoretical ideal weight, and the TCS was 25—36 % of the body weight, decreasing with increased age. The average weight of undernourished children was 68 % of the ideal weight, and the TCS 41 to 32 % of the body weight, increasing with the severity of malnutrition. When assessing the results, one should naturally always consider the patient's age, as done approximately in Fig. 1.

The results of TCS determinations performed on gastroenteritis



Table 2

Case	Sex	Age	Date	Weight	TCS as % of Body Weight	
					60'	120'
H. K.	♀	32	15/6	64 kgs	21.8	23.1
			29/6	63 "	22.1	—
J. K.	♂	29	8/6	78 "	20.6	20.5
M. P.	♀	23	28/6	54 "	23.9	—
			13/7	54 "	23.5	23.9

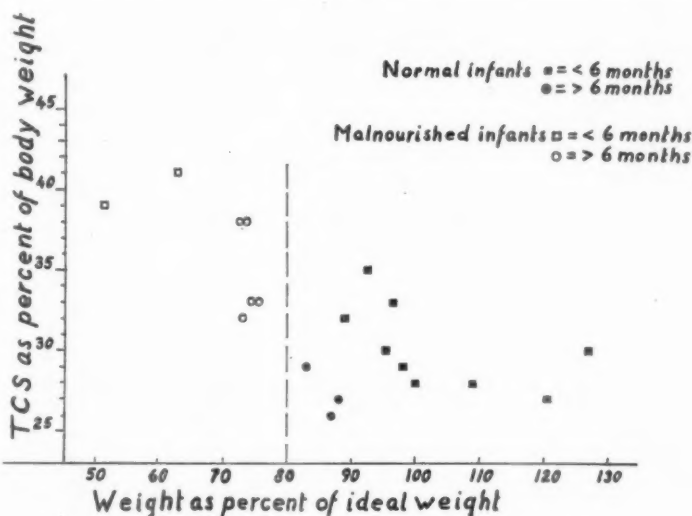


Fig. 1. Thiocyanate space in normal and malnourished infants.

patients are tabulated in Fig. 2. The ordinate illustrates the TCS as a percentage of the body weight, the abscissa showing the age of the patients in months. The individual cases are numbered according to Table 1. The parts A—F on the figure illustrate the changes which occurred in the course of the disease. To clarify matters, the figure contains normal areas with relatively broad

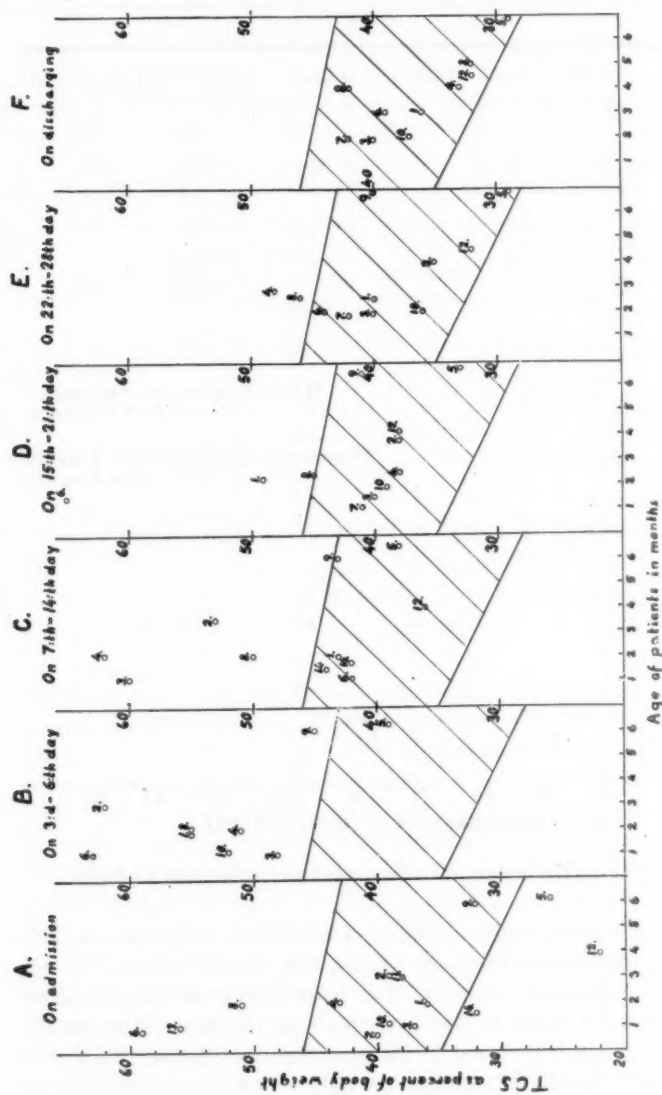


Fig. 2. Thiouranato space at various stages of severe infantile gastroenteritis. The abscissa shows the age of patients in months. Normal values in plotted area.

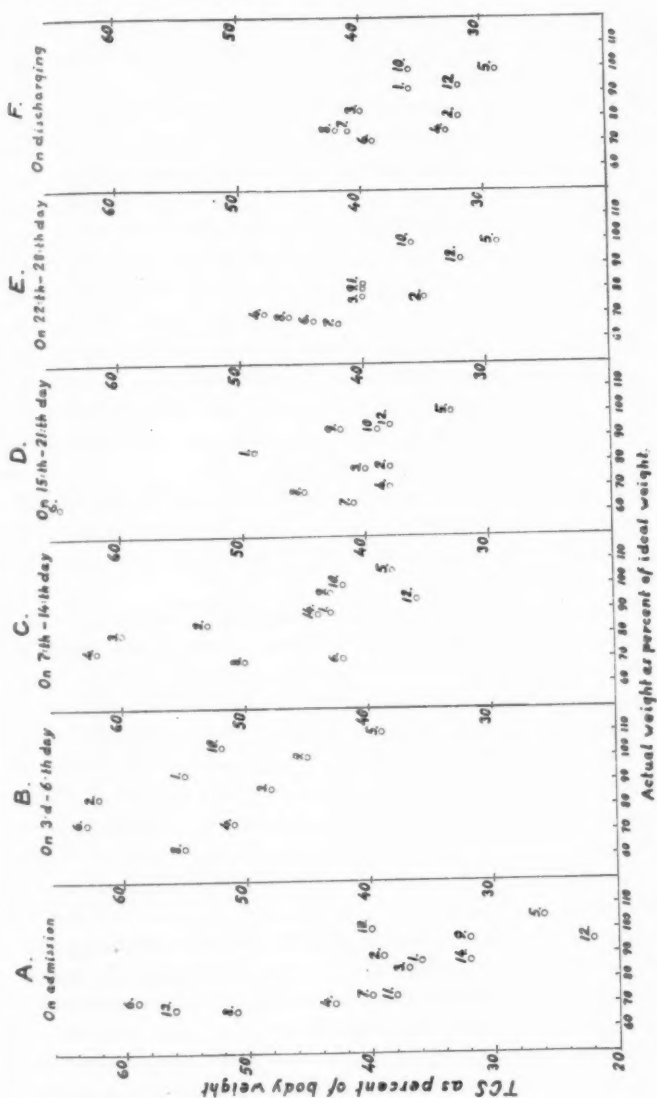


Fig. 3. Thiocyanate space at various stages of severe infantile gastroenteritis. The abscissa shows the deviation from the ideal weight.

margins obtained by different investigators (FELLERS et al., FLEXNER et al., KERPEL-FRONIUS and KOVACH, SCHNEEGANS, ROBINOW and HAMILTON, DOXIADES et al., etc.).

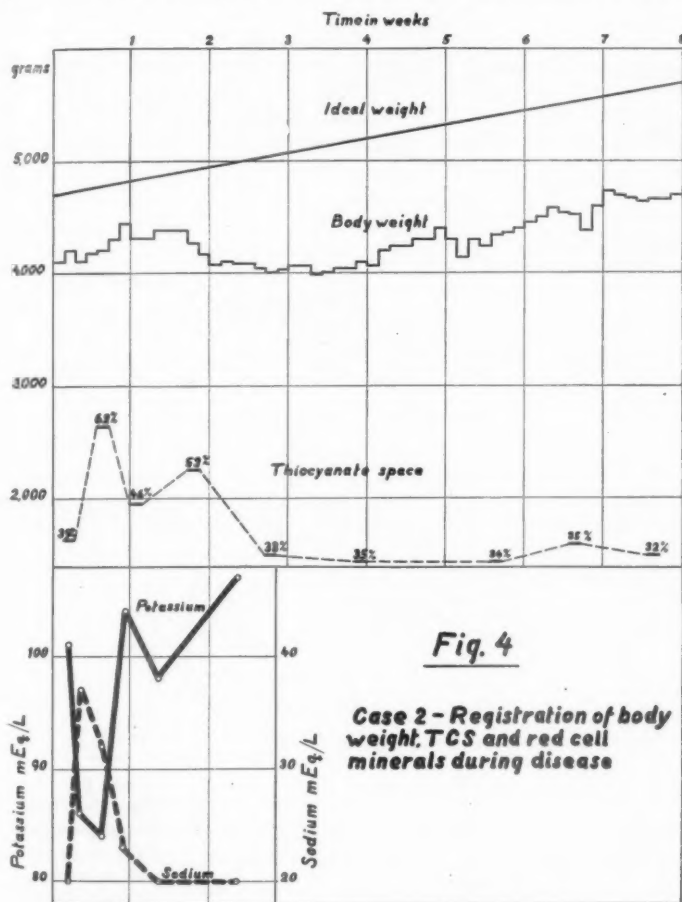
At the time the child reached hospital and the fluid therapy was instituted (A), TCS was below normal in 3 cases only. Eight patients had normal values and 3 considerably higher than normal. Clinically all these patients were at the time deeply dehydrated, as revealed also by the blood values reported above. On this basis, one would rather expect TCS values below normal in every case.

The next TCS determination was made 3 to 6 days after the beginning of treatment — clinically speaking, after rehydration (B). At this stage the TCS values were increased without exception and regularly to a higher level than presupposed by the gain in weight (Table 1). Calculated in % of the body weight, TCS surpassed the normal threshold with one exception. Yet there were no clinical findings of edema.

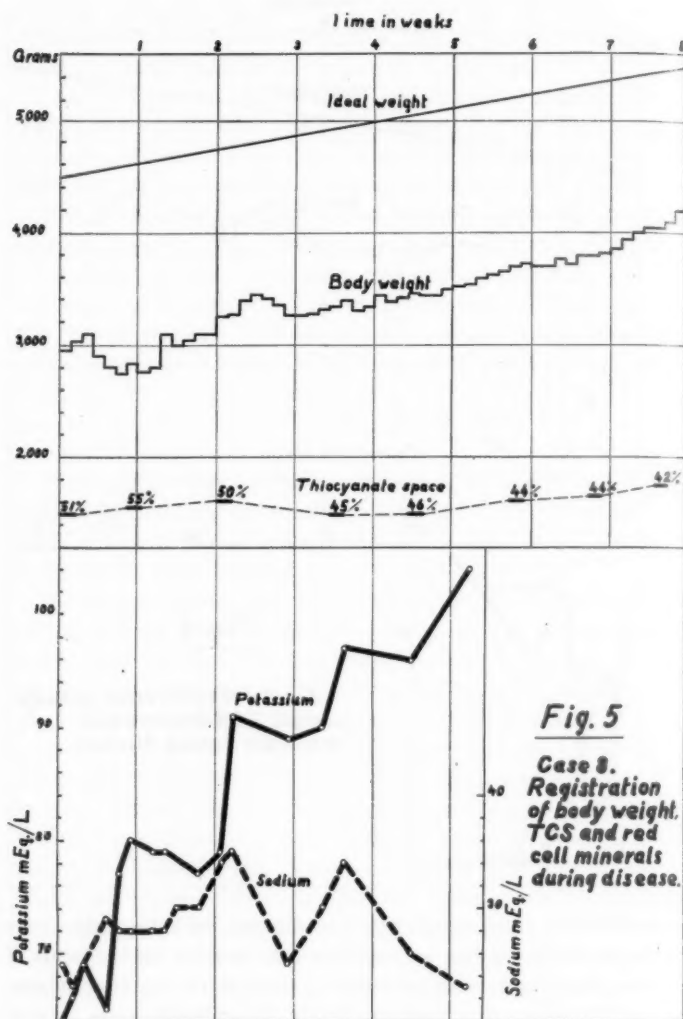
Thereafter determinations were performed every week (C—E) and the TCS values returned to normal not later than in the fifth week of treatment, all lying within the normal area at the time of discharge from hospital (F).

As already mentioned, the TCS values are affected not only by age but by nutrition as well. Fig. 3 (A—F) shows the TCS percentages obtained during the disease as compared to body weight, calculated in % of the theoretical ideal weight. In column A, i.e. while the patients were dehydrated, TCS is the higher the greater the difference between the actual and the ideal weight. After rehydration (B) a similar state of things is seen, even if TCS is now relatively higher. In the course of the following weeks (C—E) the results of the determinations approach normal values, and on discharge are (F), in relation to the weight, approximately within the limits reported by KERPEL-FRONIUS and KOVACH in their studies. It is a striking feature that in the initial stages of treatment the relative TCS values are considerably higher in many cases than could be demonstrated in states of malnutrition in the above-mentioned investigations.

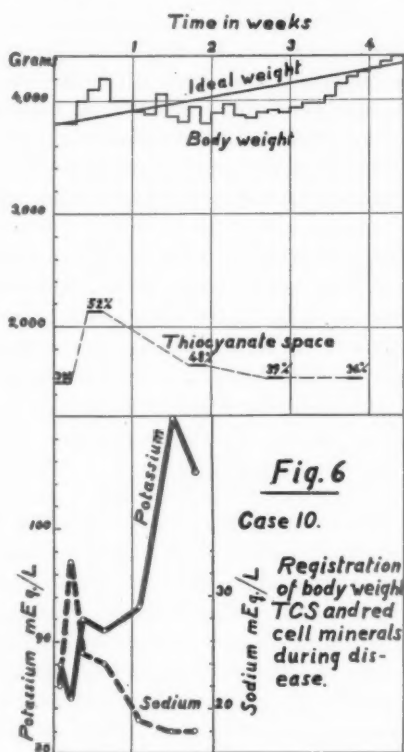
Although variations in the potassium and sodium concentration of the erythrocytes cannot, owing to the special character-



istics of these cells, be directly coordinated with the other cells in the organism, it can be considered as certain, on the basis of balance tests and tissue analyses (DARROW et al.) that during severe gastroenteritis there occurs in other bodily cells as well as in the erythrocytes a loss of potassium and accumulation of sodium. It therefore appears justified to institute a comparison

**Fig. 5**

**Case 8.**  
 Registration  
 of body weight,  
 TCS and red  
 cell minerals  
 during disease.



between the changes observed by us in red blood cells and the variations of TCS and body weight. This objective is best attained by studying some typical individual cases (Cases 2, 8 and 10).

Case 2 (Fig. 4) was a girl of 3 months who had had a normal weight prior to the onset of the disease. The potassium concentration of the erythrocytes, still normal on admission, was clearly lowered during the first days of treatment. Simultaneously, there was a rise in the sodium concentration and in TCS, both in the absolute sense and as compared to the weight. The return to normal occurred practically simultaneously both in the cellular minerals and the TCS values.

Case 8 (Fig. 5) was an undernourished baby aged 2 months who even on reaching hospital had a considerably increased TCS, an exceedingly low potassium concentration in the red blood cells, and a slightly increased sodium concentration. The gain in weight was relatively slow in the course of treatment. The absolute TCS remained the whole time on approximately the same level, and was at time of discharge consistent with values previously reported in malnutrition cases.

The third was case 10 (Fig. 6), a well developed infant of 6 weeks with the ideal weight. Apart from the low potassium and high sodium concentration of the erythrocytes at the time of admission, the case resembled in its main features those already reported. Our observations on the 8 remaining patients were fully in accordance with the typical examples described.

### Discussion

Our knowledge of the fluids contained in the body has been greatly clarified since GAMBLE's final adoption of the concepts of extracellular and intracellular fluid. In addition to analyses of the tissue minerals, attempts were made to determine extracellular fluid by substances which do not under normal conditions penetrate the cells. Sodium thiocyanate is one of those most frequently employed. In comparison with the other substances in use, thiocyanate is marked by a relatively slow excretion and as a consequence thereof by a plasma concentration which remains stable for several hours. It was found on the other hand that it is not solely extracellular, but passes to some extent e.g. into the red blood cells and the glands of the alimentary tract (CRANDALL and ANDERSON, LAVIETES et al., HOLLANDER et al., SCHWARTZ et al.). Yet these amounts are known to be insignificant and this circumstance does not, in all probability, affect the comparison of determinations made on one and the same patient.

In adults the thiocyanate values remain fairly constant. In children, and particularly in infants, they depend on their age (FLEXNER et al., FELLERS et al., etc.) and nutrition (ROBINOW and HAMILTON, KERPEL-FRONIUS and KOVACH). As also demonstrated



by the TCS values obtained by us, they are higher in respect to body weight in malnutrition than in children with a normal weight. The explanation of this phenomenon suggested by KERPEL-FRONIUS and KOVACH is that the skin is known to contain more extracellular than intracellular fluid. The surface of the skin, being considerably less reduced in malnutrition than the weight, a proportional rise of extracellular fluid is to be expected. On the other hand, the muscular mass, i.e. the system containing the largest amount of intracellular fluid, is greatly reduced in such infants.

It has been demonstrated that in certain cases the volume of TCS approaches the total amount of water in the organism. Such observations have been made in bacteremia (LING), spotted fever (HARREL), malaria and after artificial hyperpyrexia (OVERMAN, OVERMAN and FELDMAN, OVERMAN, THARP and TUTTLE). Attempts have been made to explain the phenomenon by alterations in the permeability of cells. ROBINOW and HAMILTON, in explaining the high TCS values in undernourished children, also took into account possible penetration of thiocyanate into other than erythrocytes and some glandular cells.

In our own series it is noteworthy that in a state of evident dehydration TCS was below normal only in 3 cases of 14. In another 3 cases it was, on the contrary, considerably higher. Subsequent to rehydration TCS was regularly increased, and always to a higher degree than that which would correspond to the gain in weight. We stress once more that there was no clinical evidence of edema. Towards the end of the second week of treatment, and sometimes even later, values were manifested which approached the total amount of water in the body.

It is well known that when dehydration sets in, changes occur in the first instance in the extracellular fluid and its minerals. Our patients, however, were all suffering from severe gastroenteritis which probably even involved the cells themselves. ROBINOW and HAMILTON have drawn attention to edema revealed by autopsy in similar cases diagnosed clinically as dehydration. Similar observations were also made microscopically by AHVENAINEN in several autopsies performed at our hospital on gastroenteritis

patients. Yet the highest TCS values in our series can hardly be explained as due solely to latent edema; instead, cellular permeability appears evident.

Electrolytic changes in the red blood corpuscles were pronounced in all the cases in our series, and they also indicate disturbed permeability, at least in the cells involved. On the basis of tissue analyses and balance tests performed by earlier investigators, it may be assumed that similar changes occur in other bodily cells. Considerably increased TCS values found in the conditions mentioned above have been explained by OVERMAN as due to alterations in cellular permeability produced by hyperpyrexia. In our series fever was manifested only as an exception, nor was there any correlation between it and the TCS changes.

On the other hand, dehydration and frequently acidosis are typical phenomena in severe infantile gastroenteritis, and they could be observed in our patients as well. It is a certainty that they also affect tissue cells. Possible disturbances in the suprarenal function may also have their own significant share in the alteration of fluid and minerals in these patients.

### Summary

1. A study is made of the extracellular (thiocyanate) space and blood chemistry in 14 cases of severe infantile gastroenteritis.
2. On admission, and in spite of evident dehydration, thiocyanate space was normal in 8 cases, considerably higher than normal in 3, and below normal in 3 cases only. During rehydration thiocyanate space increased regularly, and always unmistakably more than the corresponding gain in weight. While recovery was in progress, the values returned to normal.
3. At the beginning of treatment the potassium concentration of the erythrocytes was lowered in these patients and the sodium concentration increased. A certain correlation could be observed between these values and changes in thiocyanate space.
4. It is suggested on the basis of this study that changes in cellular permeability probably occur in severe infantile gastroenteritis.

### Résumé

1. On fait une étude de l'espace extracellulaire (thiocyanate) et de la chimie du sang dans 14 cas de gastroentérite infantile grave.

2. A l'admission, et malgré une déshydratation évidente, l'espace thiocyanate était normal dans 8 cas, beaucoup plus élevé que la normale dans 3 cas et au-dessous de la normale dans 3 cas seulement. Pendant la réhydratation, l'espace thiocyanate a augmenté régulièrement et toujours manifestement plus que l'augmentation correspondante de poids. Pendant que progressait la guérison, les valeurs revenaient à la normale.

3. Au commencement du traitement, la concentration de potassium des érythrocytes de ces sujets était abaissée et la concentration de sodium augmentée. On a pu observer une certaine corrélation entre ces valeurs et les changements de l'espace thiocyanate.

4. Sur la base de cette étude, on présente l'opinion que des changements de la perméabilité cellulaire se produisent probablement dans les cas de gastroentérite infantile grave.

### Zusammenfassung

1. Die Arbeit enthält eine Studie der extrazellulären (Thiocyanat) Räume und der Blutchemie in 14 Fällen von schwerer infantiler Gastroenteritis.

2. Im Anfang waren die Thiocyanat-Räume, trotz sichtbarer Eintrocknung, in 8 Fällen normal, in 3 bedeutend grösser, in nur 3 verkleinert. Während der Rehydrierung nahmen die Thiocyanat-Räume regelmässig zu und zwar mehr als der Gewichtszunahme entsprechend, um allmählich wieder normal zu werden.

3. Im Anfang der Behandlung war die Kalium-Konzentration der Erythrozyten niedrig, die Natrium-Konzentration erhöht. Eine gewisse Korrelation zwischen diesen Werten und den Veränderungen der Thiocyanate-Räume wurde nachgewiesen.

4. Es ist auf Grund dieser Befunde wahrscheinlich, dass bei schwerer infantiler Gastroenteritis Veränderungen der Zellen-Permeabilität eintreten.

### Resumen

1. Se ha hecho un estudio del espacio extracelular (tiocianato) y de la química de la sangre en 14 casos de gastroenteritis infantil grave.

2. En la admisión, a pesar de una deshidratación evidente, el espacio tiocianato era normal en 8 casos, mucho más elevado que lo normal en 3 casos e inferior a lo normal solamente en 3 casos. Durante la rehidratación, el espacio tiocianato ha aumentado con regularidad y siempre manifestamente más que el aumento correspondiente de peso. Mientras progresaba la cura, los valores volvían a lo normal.

3. Al comenzar el tratamiento, la concentración de potasio de los eritrocitos de estos casos estaba rebajada y la concentración de sodio aumentaba. Se ha podido observar cierta correlación entre estos valores y los cambios de espacio tiocianato.

4. Basándose en este estudio, se presenta la opinión de que los cambios de la permeabilidad celular se producen probablemente en los casos de gastroenteritis infantil grave.

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## Observations on the Development of the Hypophysial-Portal System

by

KALEVI NIEMINEVA

The possible effect of the hypothalamus on hypophysial function under different conditions has been studied experimentally e.g. by UOTILA, who in abnormal conditions found changes in the function of the anterior lobe following severance of the hypophysial stalk. For instance, the rat subjected to this treatment is unable to react to cold. WESTMAN and JACOBSON in Sweden have specially described the significance of the connection between the hypothalamus and pars distalis in the gonadotropic activity of the pars distalis. An important part in the influence exercised by the hypothalamus on the secretion of the glandular part is played by the portal vein of the hypophysis, a circumstance which was first observed by POPA and FIELDING.<sup>1</sup>

The original viewpoint of POPA and FIELDING was that the blood stream had first to rise to the hypothalamic centers from the so-called glandular part, the first capillary network being then formed by the sinusoids of the pars distalis region, and the second having its site in the centers of the hypothalamus. Later their opinion was in part supported by the Italian FUMAGALLI, who, however, considered that the second network is formed in the region of the hypophysial stalk in the pars tuberalis area and the neural zone of the stalk. Yet modern literature (e.g. HAMBLEN)

<sup>1</sup> It is understood that the hypophysial-portal system has no relation whatever to the portal vein system of the liver, in spite of similarity in terminology.

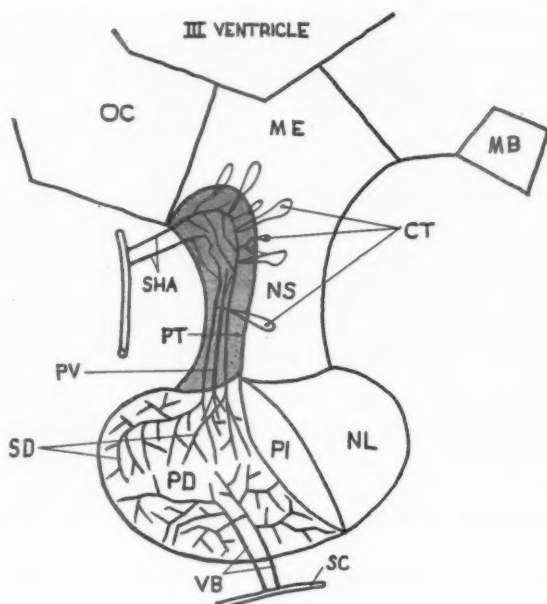


Fig. 1. Diagram illustrating the hypophyseal-portal system. PD: pars distalis; PI: pars intermedia; NL: neural lobe; PT: pars tuberalis; NS: neural stalk; ME: median eminence; OC: optic chiasma; MB: mamillary body; CT: capillary tufts; SHA: superior hypophyseal arteries; PV: portal venules; SD: sinusoids of the pars distalis; VB: vein bundles of pars distalis to sinus cavernosus (SC). According to GREEN and HARRIS.

has given recognition to the conception of WISLOCKI and KING regarding the blood supply which contradicts the theory already mentioned. This new theory has repeatedly been substantiated by such modern investigators as GREEN and HARRIS. According to it, the superior hypophyseal arteries are derived from the internal carotid and the posterior communicating arteries of each side. (Fig. 1). These arteries branch off into the sinusoid network in the region of the angle of the pars tuberalis and the optic chiasma. Capillary tufts emerge from this network into the median eminence and the region of the neural stalk. These capillary tufts are considered to be the important junction between the hypo-

thalamus and the pars distalis. The portal venules connecting the pars tuberalis network with the sinusoids of the pars distalis emerge from the network described in the vicinity of the angle of the pars tuberalis and the optic chiasma. The sinusoids of the pars distalis, in their turn, are formed into vein bundles on each side and are drained into the cavernous sinus close by.

While studying, in a different connection, the development of the density of the capillary network in fetal life, I also made some observations regarding the portal vascular system which I feel to merit a short description.<sup>1</sup>

### Material and Methods

The series consists of 12 human fetuses with a weight ranging from 100 g up to that of a fetus at term. I obtained these from professor A. Turunen at the Women's Clinic of Helsinki. It is noteworthy that these 12 were those which stained best among the original series of 30 fetuses treated in the method described below.

Fixation and staining were performed according to SJÖSTRAND's original benzidine method, with only the red blood cells staining in the vessels. Where larger fetuses were concerned, the fixation in 10 % formalin took place by stages: i.e., in the first stage the skull was opened, in the second the cerebrum was removed and lastly, in the third, the hypophysis was carefully separated. Autopsy and the ensuing fixation were often carried out immediately after death (therapeutic abortions). Autopsy was always performed within 48 hours of death at the latest, the fetuses having in the meantime been preserved in a refrigerator. Serial sections were cut, the thicknesses varying between 20—50—100  $\mu$ .

### Observations

The observations reported in this article are based on the assumption that the blood flow is directed down from the pars tuberalis. Should this assumption prove false, the terms arterioles

<sup>1</sup> Dr. RÄINÄ has encouraged me to make this investigation.



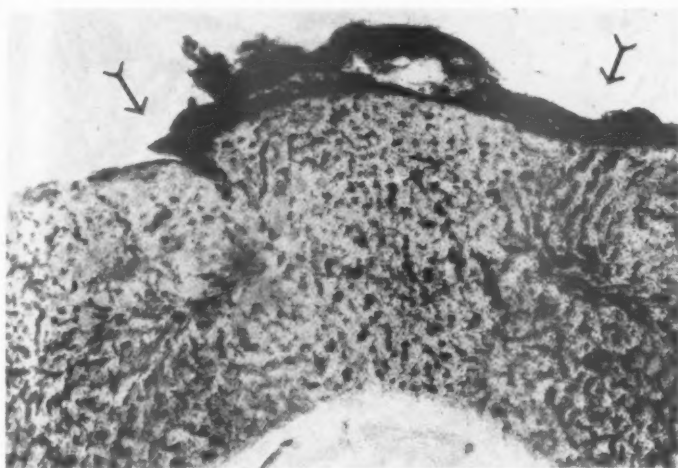


Fig. 2. Horizontal section of pars distalis. Fetus weighing 200 g, (♂). The arrows show vein groups entering the sinus cavernosus. Magnification  $\times 50$ . Thickness of section 100  $\mu$ .

and venules would have to be transposed, which naturally would not involve any essential changes in the observations as such.

As already established in a previous study of mine, the volume of blood in the pars distalis is already considerable towards the middle of the fetal period.

Fig. 2 (fetus weighing 200 g, ♂) illustrates how the sinusoids of the capillary network in the pars distalis are formed mainly into two vein bundles conveying the blood to the adjacent sinus cavernosus. The specimen is cut in the horizontal plane. In Fig. 3 (fetus weighing 520 g, ♀) the section is taken at right angles to the preceding. The genesis of the vein bundles formed by the sinusoids is clearly seen.

The portal venules are already detectable in this stage as well. With the development of fetal life, the diameters of these venules show a rapid growth. In fetuses weighing 100—200 g the largest diameters of these venules were 10—15  $\mu$  (in the absolute meaning the values must be taken with a certain reservation; e.g. the shrink-

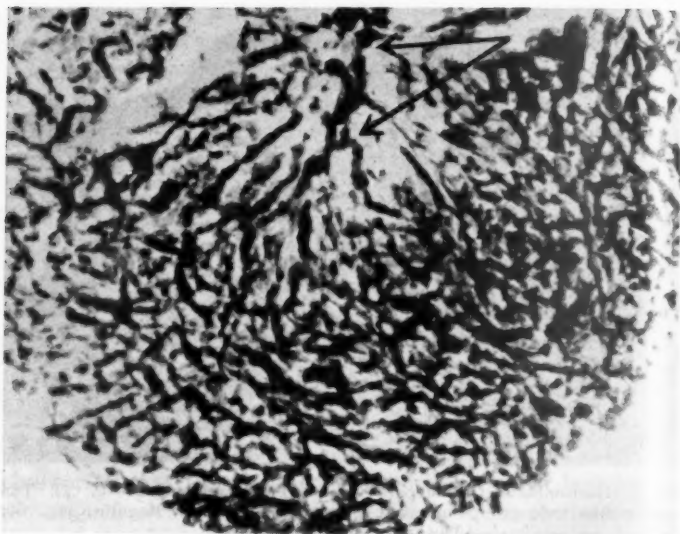


Fig. 3. Sagittal section of pars distalis. Fetus weighing 520 g (♀). The arrows mark place of junction of sinusoids. Magnification  $\times 60$ . Thickness of section  $50\mu$ .

ing coefficient has not been taken into account, owing to the nature of the investigation). The larger portal venules of fetuses at term had an average diameter of  $50-60\mu$ . Fig. 4 (fetus weighing 800 g, ♂) shows the portal venules near the borderline between the pars distalis and hypophysial stalk and, on the other hand, between the pars distalis and pars tuberalis. The section was taken in a horizontal plane. Fig. 5 (fetus weighing 2 730 g, ♂) illustrates the capillary tufts emerging from the region of the first (upper, in the pars tuberalis) sinusoid network of the hypophysial-portal system and passing into the nerve tissue of the median eminence. Since by the method employed the red cells alone were stained, it is impossible to determine in more detail the direction in which the blood vessels were going, but the vessels in question clearly have two branches, both connecting with the sinusoid network already mentioned. Fetuses at term seem to

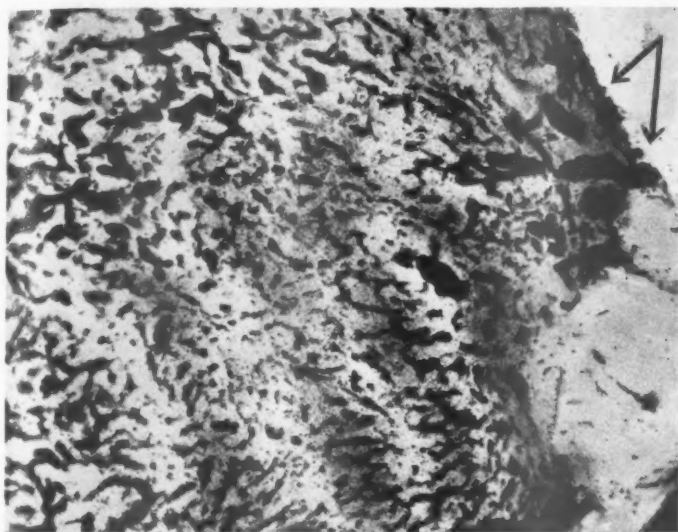


Fig. 4. Horizontal section of the hypophysis. Fetus weighing 800 g (♀). The arrows show cross-section of portal venules entering the pars distalis. Magnification  $\times 60$ . Thickness of section  $100\ \mu$ .

have an abundance of these bundles. Fig. 6 shows the region of Fig. 5 under a slighter magnification. In smaller fetuses, on the other hand, these bundles are clearly different as to quality and number. They are generally short, and their cross-sections exhibit as a rule only simple rows of red cells (Fig. 7 and 8), although the sections taken elsewhere are considerably engorged. Fig. 4 reveals the considerable hypophyseal engorgement of the fetus, from whom the sections represented in Fig. 7 and 8 were also taken.

The smallest fetus examined by me did not reveal any of the aforementioned capillary tufts. Fig. 9 (fetus weighing 120 g, ♂) shows the upper sinusoid network of the portal system, but there is no penetration by the capillary tufts of the neural stalk, or into the region of the median eminence in the sections.

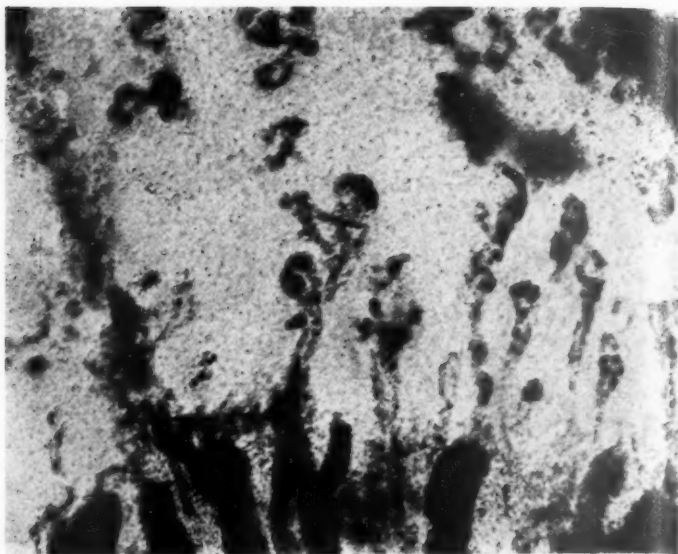


Fig. 5. Horizontal section, at a slanting angle to the plane, taken on the level of the border-line between hypophyseal stalk and median eminence. Fetus weighing 2 730 g (♂). Capillary tufts can be seen penetrating from the pars tuberalis into the region of median eminence. Magnification  $\times 100$ . Thickness of section  $100\ \mu$ .



Fig. 6. Region illustrated on fig. 5 at a lesser magnification. Magnification  $\times 20$ . Thickness of section  $100\ \mu$ .

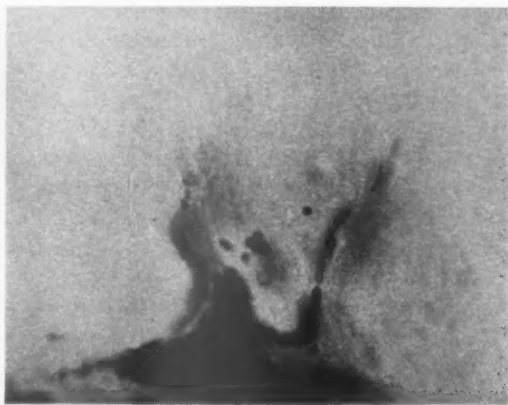


Fig. 7. Horizontal section of hypophyseal stalk. Fetus weighing 800 g (♀). Fine capillaries penetrating the neural stalk region from the sinusoid group of the pars tuberalis seen below. Magnification  $\times 320$ . Thickness of section  $100\ \mu$ .

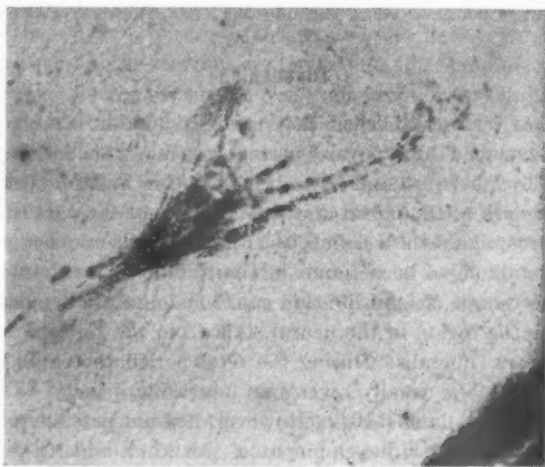


Fig. 8. As fig. 7. Capillary bundles can be seen. Magnification  $\times 175$ . Thickness of section  $50\ \mu$ .

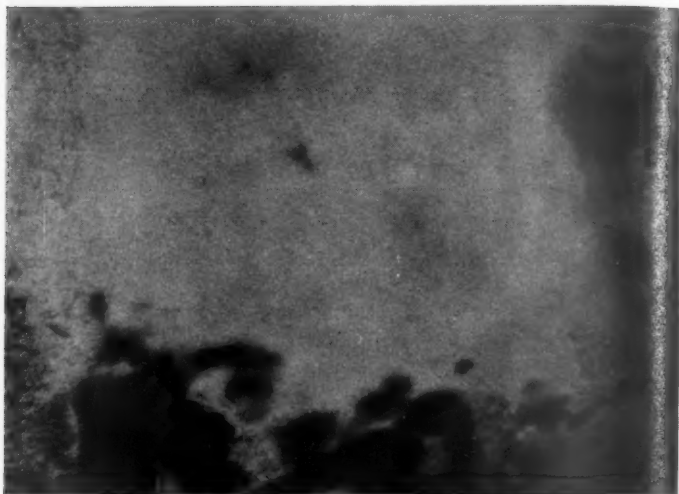


Fig. 9. Horizontal section at the level of the border-line of hypophysial stalk and median eminence. Fetus weighing 120 g (♂). Below the sinusoids of pars tuberalis, above the nerve tissue. The fig. illustrates corresponding place as fig. 5. Differs in magnification. Magnification  $\times 400$ . Thickness of section  $100\mu$ .

### Discussion

It has been established that newborn human fetuses have a fully developed hypophysial-portal system. This has been described by WISLOCKI and KING. On the other hand, no first capillary network of the portal system (sinusoids of the pars tuberalis) and no capillary tufts connecting the median eminence and the neural stalk have been found in the middle of the fetal period. At a later stage of fetal life thin capillary loops are demonstrable, entering the region of the neural stalk from the sinusoid network of the pars tuberalis. During the fetal period the capillary network in humans usually reveals an increasing density, as demonstrated by MALI and RÁIHÄ. However, it is not possible to discuss in this connection a development of this kind, which the author has proved to exist in the hypophysial region, since it is clear that we are dealing with a peculiar phenomenon, dissociated from

the general development of the blood vessels. Towards the middle of the fetal period, on the other hand, the other parts of the portal system already mentioned are in a well-developed state.

This finding, that the connecting link between the portal system and the median eminence as well as the neural stalk (hypothalamus), i.e. the tufted capillary vessels already described, develops first towards the end of the fetal period indicates that if it is true that the function of the pars distalis is regulated neuro-vascularly from the hypothalamus, this regulation reaches its full intensity only in the latest stage of fetal life. The late development of these tufts is natural, even owing to the circumstance that Rathke's pocket develops sufficiently for the formation of the macroscopic position of the hypophysis as late as towards the fourth month of fetal life, when the glandular part is immediately and organically connected with the region of the median eminence of the hypothalamus.

UOTILA's opinion that the hypothalamus regulates the pars distalis function, above all in abnormal cases, is consistent with the findings of this investigation, since it must be assumed that in fetal life the function of the pars distalis is entirely independent of variations due to external factors, and the finer regulation of the function by the nervous centers would then be unnecessary. In addition, the gonads probably do not function in fetal life (as compared to adult life); therefore the control emanating from the hypothalamus in this respect as described by WESTMAN and JACOBSON is obviously without significance in the fetal period.

On the other hand, the late development of the hypophysial-portal system is also a link in the deficient development of the premature organism, causing the exceptional organic functions of premature infants and their lowered power of resistance to external life.

### Summary

The writer found that the hypophysial-portal system is fully developed in human fetuses at term. About the middle of the fetal period, on the other hand, the capillary tufts essential to this system which penetrate from the sinusoids of the pars tuberalis

into the region of the median eminence and the neural stalk are not demonstrable. As fetal life progresses the formation of these vessel tufts can be seen.

It is concluded that if the hypothalamus regulates the function of the pars distalis by neurovascular channels, this regulation begins as late as towards the end of the fetal period.

### Résumé

L'auteur a constaté que le système portal hypophysaire est entièrement développé chez les foetus humains à terme. Au milieu de la période foetale, d'autre part, les ramifications capillaires essentielles pour ce système, qui viennent des sinusoides de la pars tuberalis vers la région de l'éminence médiane et la tige nerveuse ne peuvent être mises en évidence. Au fur et à mesure que progresse la vie foetale, la formation de ces ramifications de vaisseaux peut être observée.

On conclut que si l'hypothalamus règle la fonction de la pars distalis par des canaux neurovasculaires, cette régulation ne commence que vers la fin de la période foetale.

### Zusammenfassung

Verfasser fand, dass das Hypophysen-Portal-System beim ausgetragenen Neugeborenen voll entwickelt ist. In der Mitte der foetalen Entwicklung dagegen sind die kapillären Verbindungen zwischen den Gefäßen der Pars tuberalis und der mittleren Region, sowie dem Stiel nicht nachweisbar, was dagegen beim älteren Foetus der Fall ist. Es folgt daraus, falls die Funktion der Pars distalis vom Hypothalamus durch neurovaskuläre Verbindungen reguliert wird, dass dann diese Regulation erst am Ende der Foetalperiode anfängt.

### Resumen

El autor ha comprobado que el sistema portal de la hipófisis está enteramente desarrollado en los fetos humanos al final de la gestación. En medio del período fetal, por otra parte, las ramificaciones capilares esenciales de este sistema, que penetran de las sinusoides de la parte tuberal en la región de la eminencia media



y el tronco nervioso, no pueden ser demostradas. La formación de estas ramificaciones de vasos puede ser observada a medida que progresa la vida fetal.

Se concluye que si el hipotálamo regula la función de la parte distal por dos canales neurovasculares, esta regulación no comienza más que hacia el fin del período fetal.

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## **On the Copper Content in Mother's Milk Before and After Intravenous Copper Administration<sup>1</sup>**

by

**SVEN MUNCH-PETERSEN**

The object of the present work has been to examine the copper content of mother's milk and to find out whether it may be enhanced by artificially increasing the copper content of serum.

### **Own Investigations**

#### **Methods**

The copper concentration in the milk was determined by means of the colour reaction with sodium diethyldithiocarbamate, the procedure being essentially the same as for serum (4). 1 ml. milk was used and duplicate determinations were carried out. Owing to the richness of fat in milk an acid mixture with 20 volume % concentrated sulphuric acid was used instead of 15 % as in the case of serum. On account of the content of calcium and phosphate in the milk EDEN & GREEN (1) add sodium citrate before the alkalization which precedes the addition of sodium diethyldithiocarbamate. In this way precipitation of the copper with the calcium phosphate is avoided. As, however, the results for milk copper in the author's experiments were the same with or without the addition of citrate, this precaution was omitted. A known added amount of 100  $\gamma$  % copper was completely recovered. The mother's milk examined was milked directly into glasses cleaned

<sup>1</sup> I am indebted to the "Nordisk Insulinfond" for a grant received for this work.

with hydrochloric acid. Then they were covered with paraffined corks. Before analysis of the samples they were carefully mixed by shaking.

### Case Material

The case material, from the Maternity Hospital in Jutland (Århus), consisted of 17 healthy nursing mothers.

In 10 of these persons the variation in the copper content of the milk was examined without administration of copper.

In the 7 remaining persons the copper content in milk before and after intravenous administration of 10 to 20 cgs. of Ebosal, a water-soluble, complex copper compound (cuprous allylthio-benzoic sodium) containing 19 % copper, was investigated.

### Results and Discussion

The results of our copper determinations in mother's milk may be seen in Tables 1 and 2.

In persons 1 to 5 and 11 to 17 the copper content was examined 68 times, both at the beginning and at the end of a milking. The average of the values from the beginning is  $53.99 \gamma \% \pm 10.95$  and from the end  $55.04 \gamma \% \pm 13.33$ . The difference between the two averages is only 0.50 times the standard deviation of the difference, which is not significant. As no certain difference between the value at the beginning and that at the end of the milking was demonstrated the average was used in these cases. On the other milk samples only one determination was performed (in samples from the beginning of a milking).

In Table 1 are given the copper content values of persons who did not have Ebosal. It appears that from some of the subjects only a single sample was available, whereas from other subjects there were numerous samples spread over several days. Considerable variations from individual to individual may be observed (limits from the fourth day after delivery: 20 to  $84 \gamma \%$ ). In the same person the copper content was, however, fairly constant, although a pronounced fall in the copper concentration was observed on the second and third days after labour.

Table 1.

The Copper Content in Mother's Milk From Persons Without Administration of Ebosal.

Case No.	Date	Day in Puerperium	Hour	Copper in $\gamma/\gamma$ in the Separate Milkings
1	May 7, 1948	6	7.30 a.m.	48
2	May 7, 1948	6	7.30 a.m.	57
3	May 21, 1948	4	4.30 p.m.	47
4	May 21, 1948	7	4.30 p.m.	66
5	June 11, 1948	6	7.30 a.m.	71
"	"	"	10.30 a.m.	74
"	"	"	1.30 p.m.	65
"	"	"	4.30 p.m.	71
6	Nov. 30, 1949	4	10.30 a.m.	47
"	"	"	4.30 p.m.	42
"	Dec. 1, 1949	5	10.30 a.m.	60
"	"	"	4.30 p.m.	60
"	Dec. 2, 1949	6	10.30 a.m.	61
"	"	"	4.30 p.m.	59
"	Dec. 3, 1949	7	10.30 a.m.	66
"	"	"	4.30 p.m.	62
"	Dec. 4, 1949	8	10.30 a.m.	60
"	"	"	4.30 p.m.	56
7	Nov. 30, 1949	3	10.30 a.m.	15
"	"	"	4.30 p.m.	17
"	Dec. 1, 1949	4	10.30 a.m.	25
"	"	"	4.30 p.m.	31
"	Dec. 2, 1949	5	10.30 a.m.	33
"	"	"	4.30 p.m.	35
"	Dec. 3, 1949	6	10.30 a.m.	47
"	"	"	4.30 p.m.	42
"	Dec. 4, 1949	7	10.30 a.m.	58
"	"	"	4.30 p.m.	52
8	Experiment started 33 hours after labour.			
"	Dec. 19, 1949	2	10.30 a.m.	19
"	"	"	4.30 p.m.	12
"	Dec. 20, 1949	3	10.30 a.m.	9
"	"	"	4.30 p.m.	10

Table 1 (Cont.).

Case No.	Date	Day in Puerperium	Hour	Copper in $\gamma\%$ in the Separate Milkings
8	Dec. 21, 1949	4	10.30 a.m.	23
"	"	"	4.30 p.m.	28
"	Dec. 22, 1949	5	10.30 a.m.	43
"	"	"	4.30 p.m.	40
"	Dec. 23, 1949	6	10.30 a.m.	48
"	"	"	4.30 p.m.	49
"	Dec. 24, 1949	7	10.30 a.m.	51
"	"	"	4.30 p.m.	54
"	Dec. 25, 1949	8	10.30 a.m.	52
"	"	"	4.30 p.m.	51
"	Dec. 26, 1949	9	10.30 a.m.	53
"	"	"	4.30 p.m.	48
"	Dec. 27, 1949	10	10.30 a.m.	47
"	"	"	4.30 p.m.	42
"	Dec. 28, 1949	11	10.30 a.m.	46
"	"	"	4.30 p.m.	44
"	Dec. 29, 1949	12	10.30 a.m.	41
"	"	"	4.30 p.m.	33
"	Dec. 30, 1949	13	10.30 a.m.	43
"	"	"	4.30 p.m.	43
"	Dec. 31, 1949	14	10.30 a.m.	45
"	"	"	4.30 p.m.	43
"	Jan. 1, 1950	15	10.30 a.m.	40
"	"	"	4.30 p.m.	44
9	Experiment started 24 hours after labour.			
"	Dec. 19, 1949	1	4.30 p.m.	87
"	Dec. 20, 1949	2	10.30 a.m.	39
"	"	"	4.30 p.m.	37
"	Dec. 21, 1949	3	10.30 a.m.	49
"	"	"	4.30 p.m.	52
"	Dec. 22, 1949	4	10.30 a.m.	67
"	"	"	4.30 p.m.	61
"	Dec. 23, 1949	5	10.30 a.m.	68
"	"	"	4.30 p.m.	65
"	Dec. 24, 1949	6	10.30 a.m.	84
"	"	"	4.30 p.m.	79

Table 1 (Cont.).

Case No.	Date	Day in Puer-perium	Hour	Copper in % $\gamma$ in the Separate Milkings
9	Dec. 25, 1949	7	10.30 a.m.	73
"	"	"	4.30 p.m.	72
"	Dec. 26, 1949	8	10.30 a.m.	76
10	Experiment started 10 hours after labour.			
"	Dec. 20, 1949	1	4.30 p.m.	43
"	Dec. 21, 1949	2	10.30 a.m.	42
"	"	"	4.30 p.m.	34
"	Dec. 22, 1949	3	10.30 a.m.	10
"	"	"	4.30 p.m.	11
"	Dec. 23, 1949	4	10.30 a.m.	20
"	"	"	4.30 p.m.	24
"	Dec. 24, 1949	5	10.30 a.m.	36
"	"	"	4.30 p.m.	39
"	Dec. 25, 1949	6	10.30 a.m.	45
"	"	"	4.30 p.m.	44
"	Dec. 26, 1949	7	10.30 a.m.	43
"	"	"	4.30 p.m.	43
"	Dec. 27, 1949	8	10.30 a.m.	43
"	"	"	4.30 p.m.	43
"	Dec. 28, 1949	9	10.30 a.m.	46

In Table 2 are seen the values of milk copper before and after intravenous administration of Ebeseal. A comparison of milk samples taken before and after administration of Ebeseal and at corresponding times showed almost unchanged conditions in five women, whereas one case (No. 15) showed a decided falling and one (No. 16) a rising tendency. The fluctuations observed can hardly be ascribed to administration of copper (cf. the variations which occur without copper intake). The averages of the copper content in mother's milk before and after administration of Ebeseal are  $53.79 \gamma \% \pm 12.60$  and  $54.24 \gamma \% \pm 10.59$ , respectively. The difference is not significant, amounting only to 0.15 times standard deviation of the difference. There is, thus, no reason to assume

Table 2.

The Copper Content in Mother's Milk From Persons With Administration of Ebesal.

Case No.	Date	Day in Puer-perium	Hour	Copper in $\gamma$ % in the Sepa-rate Milkings
11	Before administration of Ebesal.			
"	May 28, 1948	8	1.30 p.m.	49
	After administration of 0.10 g. Ebesal at 3.30 p.m.			
"	May 28, 1948	8	4.30 p.m.	52
12	Before administration of Ebesal.			
"	June 3, 1948	6	1.30 p.m.	41
	After administration of 0.10 g. Ebesal at 2.00 p.m.			
"	June 3, 1948	6	4.30 p.m.	37
13	Before administration of Ebesal			
"	June 8, 1948	6	7.30 a.m.	42
	After administration of 0.10 g. Ebesal at 8.00 a.m.			
"	June 8, 1948	6	10.30 a.m.	51
"	"	"	1.30 p.m.	43
"	"	"	4.30 p.m.	47
14	Before administration of Ebesal.			
"	June 17, 1948	7	7.30 a.m.	42
"	"	"	10.30 a.m.	42
"	"	"	1.30 p.m.	46
"	"	"	4.30 p.m.	48
	After administration of 0.20 g. Ebesal the following day at 7.15 a.m.			
"	June 18, 1948	8	7.30 a.m.	47
"	"	"	10.30 a.m.	36
"	"	"	1.30 p.m.	41
"	"	"	4.30 p.m.	44
15	Before administration of Ebesal.			
"	July 17, 1948	6	7.30 a.m.	84
"	"	"	10.30 a.m.	81
"	"	"	1.30 p.m.	76
"	"	"	4.30 p.m.	86

Table 2 (Cont.).

Case No.	Date	Day in Puer-perium	Hour	Copper in % in the Separate Milkings
15	After administration of 0.20 g. Ebesal the following day at 7.15 a.m.			
"	July 18, 1948	7	7.30 a.m.	72
"	"	"	10.30 a.m.	67
"	"	"	1.30 p.m.	57
"	"	"	4.30 p.m.	64
16	Before administration of Ebesal.			
"	Oct. 26, 1949	5	7.30 a.m.	61
"	"	"	10.30 a.m.	57
"	"	"	1.30 p.m.	57
"	"	"	4.30 p.m.	57
"	"	"	7.30 p.m.	59
"	Oct. 27, 1949	6	1.30 a.m.	55
	After administration of 0.20 g. Ebesal Oct. 27 at 7.00 a.m.			
"	Oct. 27, 1949	6	7.30 a.m.	62
"	"	"	10.30 a.m.	65
"	"	"	1.30 p.m.	68
"	"	"	4.30 p.m.	73
"	"	"	7.30 p.m.	72
"	Oct. 28, 1949	7	1.30 a.m.	67
17	Before administration of Ebesal.			
"	Oct. 31, 1949	5	7.30 a.m.	47
"	"	"	10.30 a.m.	44
"	"	"	1.30 p.m.	51
"	"	"	4.30 p.m.	47
"	"	"	7.30 p.m.	48
"	Nov. 1, 1949	6	1.30 a.m.	46
"	Nov. 1, 1949	6	7.30 a.m.	51
"	"	"	10.30 a.m.	47
"	"	"	1.30 p.m.	48
"	"	"	4.30 p.m.	46
"	"	"	7.30 p.m.	51
"	Nov. 2, 1949	7	1.30 a.m.	51



Table 2 (Cont.).

Case No.	Date	Day in Puerperium	Hour	Copper in $\gamma$ % in the Separate Milkings
After administration of 0.20 g. Ebeseal Nov. 2 at 7.00 a.m.				
17	Nov. 2, 1949	7	7.30 a.m.	51
"	"	"	10.30 a.m.	49
"	"	"	1.30 p.m.	47
"	"	"	4.30 p.m.	46
"	"	"	7.30 p.m.	47
"	Nov. 3, 1949	8	1.30 a.m.	52
"	Nov. 3, 1949	8	7.30 a.m.	52
"	"	"	10.30 a.m.	52
"	"	"	1.30 p.m.	48
"	"	"	4.30 p.m.	53
"	"	"	7.30 p.m.	44
"	Nov. 4, 1949	9	1.30 a.m.	57

that Ebeseal administered is secreted with the milk, nor is there any basis for supplying the child with copper in this way.

It should be noted that the amounts of Ebeseal administered have undoubtedly involved a considerable rise in the copper content of serum. This appears from investigations of five subjects which after intravenous administration of 5 to 10 cgs. Ebeseal were followed up to six hours (Fig. 1). In one of the nursing women only (No. 9) was there any possibility of carrying out a control examination. In this case the serum copper was already much increased (to 236  $\gamma$  %) before administration of copper, as in the case of pregnancy and puerperium, but five minutes after intravenous administration of 20 cgs. Ebeseal an increase to 480  $\gamma$  % was observed.

The average of 115 milk samples (without administration of Ebeseal) from the first week of the puerperium is  $48.37 \gamma \% \pm 16.59$ . As the child receives about  $1\frac{1}{2}$  l. milk per day during the first week, this means that nursing involves a daily loss of about  $\frac{1}{4}$  mg. copper.

The results obtained for the copper content in mother's milk

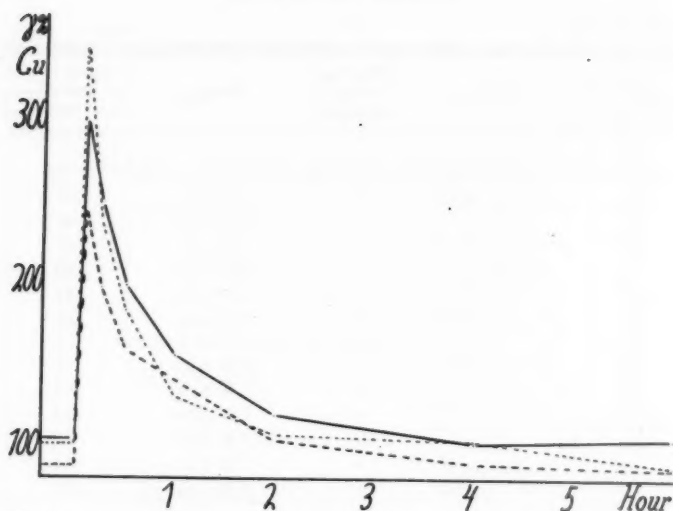


Fig. 1. Serum copper values immediately before and up to six hours after intravenous intake of 5 cgs. Ebetal in three persons. In two other persons, who had 10 cgs. Ebetal administered intravenously, the copper content in one was 103  $\gamma$  % before and 387  $\gamma$  % 5 min. after the copper intake and in the other 98  $\gamma$  % and 409  $\gamma$  %, respectively. Case 1: —. Case 2: — — —. Case 3: ·····.

harmonize well with previous investigations. By the cystein method of Warburg ZONDEK & BANDMANN (6) thus found 50 to 60  $\gamma$  % in 70 milk samples from women in the first and second months of lactation. GORTER, GRENDL & WEYERS (2) and LESNÉ & BRISKAS (3), who both employed sodium diethyldithiocarbamate, found, respectively, a little lower values: 21 to 28  $\gamma$  %, and a little higher values: 60 to 95  $\gamma$  % (second month of lactation) than I did. LESNÉ & BRISKAS observed a falling trend in the copper concentration of mother's milk during the period of lactation, colostrum containing 95 to 123  $\gamma$  %, whereas the values in the ninth month of lactation were 30 to 70  $\gamma$  %. Examinations of a possible transference of Ebetal from mother to child through the milk had not been carried out previously.

The investigators mentioned have also determined the copper content in cow's milk, in which ZONDEK & BANDMANN found 15

to 20  $\gamma$  %; GORTER, GREDEL & WEYERS 9 to 14  $\gamma$  %; and LESNÉ & BRISKAS 9 to 50  $\gamma$  %. In spite of the wide variations in the statements it is thus agreed that the copper content in cow's milk is essentially lower than in mother's milk. Our own investigations (5) confirm this finding, the average for copper content in cow's milk being 5.53  $\gamma$  % (in mother's milk: 48.37  $\gamma$  %).

### Summary

1) The copper content in mother's milk is on an average about 50  $\gamma$  % which is essentially higher than that given for cow's milk.

2) Investigations of the copper content in mother's milk before and after artificial increase of serum copper by intravenous administration of Ebesal show no changes in the copper concentration of the milk.

### Résumé

1) La quantité de cuivre dans le lait de femme est en moyenne de 50  $\gamma$  % environ, c'est à dire beaucoup plus élevée que celle indiquée pour le lait de vache.

2) Des recherches sur la quantité de cuivre dans le lait de femme faites avant et après une augmentation artificielle du cuivre de sérum d'Ebesal par injection intraveineuse n'indique pas de changements de la concentration du cuivre dans le lait.

### Zusammenfassung

1) Der Kupfergehalt in Muttermilch ist durchschnittlich etwa 50  $\gamma$  %, das heisst wesentlich grösser als der von Kuhmilch.

2) Untersuchungen über den Kupfergehalt in Muttermilch vor und nach künstlicher Erhöhung des Serumkupfers durch intravenöse Eingabe von Ebesal zeigen keine Änderungen der Kupferkonzentration der Milch.

### Resumen

1) La cantidad de cobre en la leche de mujer es alrededor de 50  $\gamma$  %, es decir, mucho mas elevada que la indicada en la leche de vaca.

2) Las investigaciones sobre la cantidad de cobre en la leche de mujer hechas antes y después de un aumento artificial del cobre en el suero por inyección endovenosa de Ebosal, no indican cambios de concentración del cobre en la leche.

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## Familial Occurrence of Necrosis Adiposa Neonatorum

by

TORBEN JERSILD and AXEL PERDRUP

Necrosis adiposa neonatorum (GELBJERG-HANSEN, 1926) — synonyms: adiponecrosis subcutanea neonatorum and subcutane Fettgewebsnekrosen beim Neugeborenen — must be looked upon as a rare affection. In the literature only about 100 cases have been described; in Denmark, since 1918, altogether 13 cases have been reported. A comprehensive review of the literature has been given by BOJLEN & PETRI (1936).

The disease appears as subcutaneous infiltration, varying in extension and localization, in infants. These infiltrations are of india-rubber consistency and vary in size from that of small grains to that of a halfpenny. The skin over the nodules may be a little more bluish or more whitish than normal skin, but it may also be normal in color. Dermographism is sometimes present. The general condition of the patients is not affected by the lesion, which subsides spontaneously, most often within some months. Histologically this condition is characterized by fat necrosis in the subcutaneous tissue. This is illustrated very well by the case to be described in the following.

The etiology is obscure, and many causes have been suggested. BERNHEIM-KARRER (1926) thinks that there is some connection between traumatic birth injury and the adiponecrosis and several other authors have subscribed to this view. CRUSE (1875), who was the first to describe this affection, took chilling of the skin to be the main factor in the etiology of adiponecrosis, and this might be suggested also by the case reported by REYN (1935).

Regarding traumatic birth injuries these are frequent, but the present lesion is indisputably seldom. To us it therefore seems more reasonable to assume the presence of some abnormality in the composition of the fat tissue, so that precipitation may more readily take place in the subcutaneous adipose tissue — a theory advanced by UNSHELM (1932). So far, analyses of the blood and urine have furnished no evidence as to the etiology of the disease.

### Case Record

The patient was a boy admitted at the age of 7 weeks, the last of six siblings.

He was born at home two months after term. Nevertheless the delivery was easy, after only three pains and without any artificial assistance. The child was asphyxiated for about 15 min. Birth weight 5900 g. As early as the day after birth the nurse noticed "nodules in the skin". The mother claims that large bluish and tender nodes appeared everywhere on the trunk and extremities, especially on the back, "making the child almost hunchbacked". Gradually the color of the skin became normal, the tenderness of the nodules subsided, and the skin infiltration diminished. The child was breast-fed until one month old, after which he was given an addition of 60 % milk mixture. At first he thrived well but at the age of 6 weeks he had dyspepsia, on which account, at the age of 7 weeks, he was admitted to the Pediatric Department of the Sundby Hospital.

*Physical Examination.* General condition good. Appearance of skin normal as the abnormal changes in the skin were revealed only by touching. On the trunk and extremities, especially on the buttocks and upper part of the back, the subcutaneous tissue was the site of innumerable infiltrations varying in size from that of a grain to that of a halfpenny and of a consistency like that of india-rubber. The head, scrotum, palms and soles were free from such changes. The infiltrations were movable against the underlying fascia and the epidermis appeared to be normal. On tightening of the skin over the infiltrations it presented a configuration suggestive of that of orange peel.

As may be seen in Fig. 1, the epidermis was normal in structure. In the underlying connective tissue hair follicles as well as sweat glands are seen, and more deeply, larger areas of fat tissue with fatnecrosis; occurrence of giant-cells and lipophages, with some mesodermal proliferation between the fat cells, the nuclei and cellular membranes of which stained but poorly. No increase in capillaries was seen. The giant-cells were of the foreign-body type and no lymphocytic infiltration

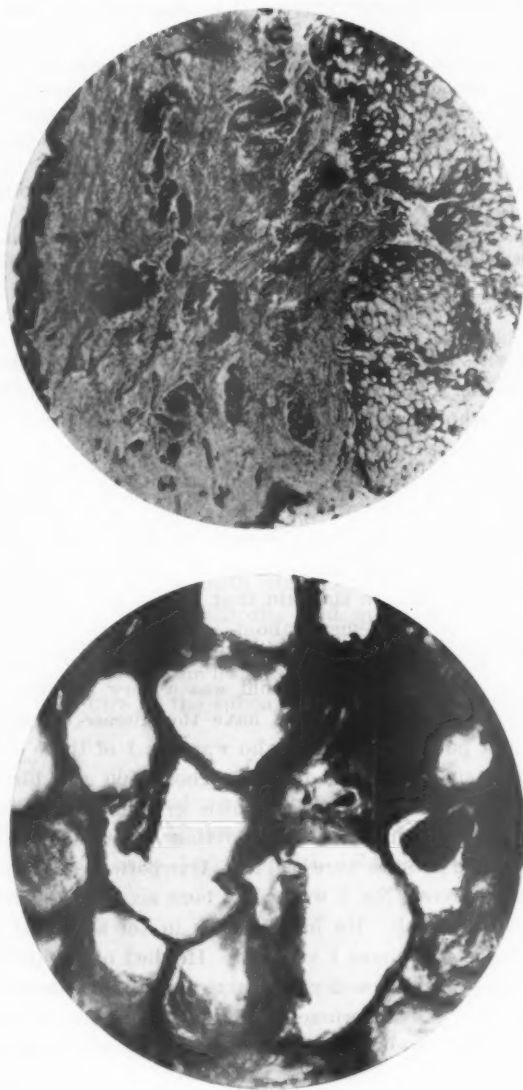


Fig. 1. Biopsy of the skin and subcutis. Low and high magnification.

was seen in the periphery. Fatty acid crystals were not seen in this specimen.

*Laboratory Tests.* — Urine: no blood, sugar, albumin or pus. Diastase normal. Blood: 90 % hemoglobin; 4,63 million erythrocytes; 8500 white blood cells. Differential count: staff nuclear neutrophils 1 %; segment-nuclear neutrophils 18 %; eosinophils 11 %; lymphocytes 63 %; monocytes 5 %; plasma cells 2 %.

Wassermann negative. Blood sugar tolerance curve: slightly flattened.

X-ray examination of the entire child: no abnormalities of the bones, no areas of calcification in the soft parts.

### Family History

The parents are divorced. No information could be obtained about the father's family. The following data were furnished by the mother, who is well acquainted with the occurrence of this disease in her family and to us seems reliable.

The great-great-grandmother of our patient was born in Berlin. Throughout her life she was troubled with a skin affection described as "elephant's skin with grains beneath it." Her first child — the great-grandmother of our patient — weighed 6,5 kg at birth and presented nodules in the skin that "gradually" disappeared. (Even though this statement about the absolute birth weight ought to be taken only with some degree of reservation, there can hardly be any doubt that the child was a very big one.) Her youngest daughter, who did not have the disease, became the mother of our patient's mother, who was No. 1 of three siblings. She was born six weeks past term, weighed 5500 g at birth and presented nodules in the skin which gradually disappeared. But she claims that she can remember that as late as in her first school year some nodules were still left. Our patient has five older brothers and sisters. No. 1 was a boy born six weeks past term, weight 4750 g at birth. He had nodules in the skin that disappeared when he was about 1 year old. He died of pneumonia at the age of 14 years. Nos. 2 and 3 were twins, born three weeks past term. No. 4 was born seven weeks past term, No. 5, two weeks past term, and our patient, as already mentioned, two months past term.



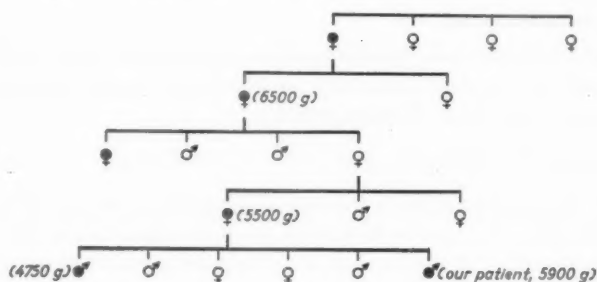


Fig. 2. Maternal pedigree of the patient.

The individuals designated by ● are stated to have had a skin affection like that of our patient. It will be noticed that in the first four generations this lesion appeared only in the firstborn — and only in females. The figures in parentheses give the birth weight.

The maternal pedigree of our patient is presented in Fig. 2.

Our case is the first one described in which the family history of the patient has shown an accumulation of such cases. In this family we also meet with an accumulation of delayed delivery and children with a high birth weight. The birth of our patient proceeded without any difficulty and apparently without any traumatic injury. On this account we find it reasonable to assume that the appearance of the lesion depends upon a constitutionally abnormal structure of the subcutaneous adipose tissue.

### Summary

A case of necrosis adiposa neonatorum is described.

The maternal side of the patient's family shows an accumulation of similar cases, together with delayed delivery and high birth weights.

### Résumé

On décrit un cas de nécrose adipeuse des nouveau-nés.

Du côté maternel, la famille du sujet montre une accumulation de cas similaires avec délivrance retardée et poids élevé à la naissance.

**Zusammenfassung**

In einem Fall von Necrosis adiposa neonatorum zeigt die Familie der Mutter eine Anhäufung ähnlicher Fälle, sowie auch Spätgeburten und hohe Geburtsgewichte.

**Resumen**

Se describe un caso de necrosis adiposa de los recién nacidos.

Por parte de la madre, la familia del sujeto muestra una acumulación de casos similares, con alumbramiento retardado y peso elevado al nacer.

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## **Myasthenia Gravis and the Thymus**

### **A Survey and the Case of a 9-Year-Old Girl**

by

**NILS TUNESTAM**

After having long been considered a very uncommon illness, myasthenia gravis pseudoparalytica (m.g.) has been diagnosed to a continually increasing extent especially during the last decade. This has been rendered possible above all by WALKER's (89) discovery of the effect of prostigmin in cases of m.g., which effect has proved valuable both therapeutically and diagnostically. Interest in this puzzling illness has further increased since thymectomy has proved in many cases to lead to appreciable improvement. The clinical and physiological research work in connection with m.g. carried on in most culture countries has already resulted in a literature which is difficult to survey. Therefore, it may be considered that there is reason to give a short survey of the present ideas on the illness in question and of the problems associated with it, in connection with a case of m.g. in a child, which was interesting in several respects.

### **Pathology**

At autopsies on m.g. patients no invariable severe anatomic or histologic changes are found, but as a rule round cell infiltration is met with in different groups of muscles, occasionally also in the central nervous system (58). There is not infrequently hypoplasia of the cortex of the suprarenal gland, as in cases of "status thymicolymphaticus." Thus m.g. differs from the majority of protracted, wasting diseases and other physically trying

conditions, which are usually accompanied by enlargement of the cortex of the suprarenal gland and reduction of the thymus and lymphoid tissue ("general adaptation syndrome") (76).

*The thymus in cases of myasthenia gravis.* WEIGERT (91) (1901) appears to have been the first to observe a thymus tumour and m.g. in the same patient. He thought it possible that the round cell infiltration in the musculature was a kind of metastasis from the primary tumour in the thymus. Increasing numbers of observations have subsequently strengthened the suspicion of a causal connection between the thymus and m.g. Among 129 cases of m.g. assembled in the literature (POER (69), 1942) the thymus was found to be normal in only 58 cases. In 30 cases there was persistence or enlargement, in 37 cases benign tumours and in 4 cases malignant tumours. Thymectomy on 32 m.g. patients at the Mayo Clinic (21) revealed tumours in 15 cases and hyperplasia of the thymus in the others, with the exception of one, where, however, the correctness of the observations was called into question. The circumstance that two such unusual conditions as m.g. and thymus changes occurred so frequently in the same individuals must be considered proof of a connection of some kind or other. For purposes of comparison, it may be mentioned that in 6 000 autopsies HOMBURGER (43) (1943) found only 41 cases of tumours or persistence in the thymus, of which 27 cases were in children under 16 years of age. Two of the adults with thymus changes had m.g.

The lack of agreement between the series cited above indicates some uncertainty as to the question of what is normal and what is pathologic in the morphology of the thymus. It appears improbable that in one large collocation the thymus should be normal in 45 % of the myasthenia gravis cases, while in the other it should exhibit severe anatomic changes in all, or nearly all, the cases, even though the last-mentioned series comprised an operation material which may thus be presumed to be selected. In the latest published and hitherto largest collocation of thymectomy in cases of m.g. KEYNES (48) (1949) describes 155 cases, of which only 18 exhibited tumours. In the other cases the weight of the thymus did not diverge significantly from its weight in healthy

persons of the same age, nor did it exhibit any relation to the degree of severity of the illness. In the study of the state of the thymus in cases of m.g. it is necessary to give some attention to the normal morphology and physiology of the organ.

*The normal anatomy and histology of the thymus.* Like the parathyroidea glands, the thymus is formed from paired diverticula from the branchial clefts in the 4th—5th embryonal weeks, mainly from the third branchial cleft, while smaller parts are possibly developed from the 4th and 5th branchial clefts. The bifidity persists as a rule, but the two lobes which are gradually formed may be joined by an isthmus. Owing to an incomplete fusion between the different anlagen, aberrant thymus tissue may be found in places in the throat or mediastinum far distant from the main part of the gland. Normally the thymus is met with behind the sternum and from the height of the cartilage of the 4th rib may extend cranially right up to the lower edge of the thyroidea — with considerable normal variations.

The weight of the thymus is relatively greatest at birth, about 15 g. It reaches its greatest absolute weight at puberty (average, according to Hammar, 36.5 g), after which the age involution begins. At the age of 25 years the average weight is 25 g and at 70 years 6 g. As the organ decreases in size, it is replaced by fat and connective tissue, but it never disappears entirely, and in old people gland tissue is found mainly in the caudal part of the gland. It may be of interest that, as in man, age involution takes place in all mammals and in fishes, but only to a slight extent in amphibians and reptiles, and not at all in birds.

The original ordinary epithelial cells of the thymus anlage gradually change into a reticular epithelium, the meshes of which are filled by invading lymphocyte-like cells, the so-called thymocytes. The latter are most numerous peripherally in the small lobuli of which the gland is built up, and which have originated from the repeated ramification of the original solid epithelial fibres. The different lobuli are connected at their deep end by a parenchymal fibre, tractus centralis thymi. Centrally in the lobuli the thymocytes are less numerous. Therefore, a darker cortical zone and a lighter medullary zone are seen in a stained section. The so-called Hassall corpuscles are typical of the thymus medulla. Their appearance seems to be due to the hypertrophy of single epithelial cells, at which other epithelial cells become more or less flattened and are successively deposited concentrically outside the central cell. Degenerative changes gradually appear centrally in the corpuscles, the nucleus shrivels and becomes pyknotic, the cell bodies shrivel and become hyalinized. Finally they disintegrate during an invasion of leukocytes.

During the involution of the thymus, histologic changes in the organ also take place. The cortex is reduced considerably in relation to the

medulla. The Hassal corpuscles, which at birth are estimated at about 1 million and at puberty at about  $1\frac{1}{2}$  million, then rapidly decrease in number. In old people only a few relatively large Hassal corpuscles are to be seen.

WEISE (92, 93) (1939) considers that he has been able to prove that the apparently chaotic masses of epithelium really form typical small groups, which he calls primitive bodies. They are said to consist of cubic or cylindric epithelium facing towards a fine lumen and surrounded by a basal membrane. They are said to have a limited lifetime, but new primitive bodies are said to be formed continuously during the whole period, the numbers being dependent on the degree to which the products of the gland are called upon. During regressive changes they are changed back into Hassal corpuscles, which thus are not active elements, but owing to their numbers could afford information as to the functional condition of the organ.

*The pathology of the thymus.* Apart from the normal age involution of the thymus, an incidental involution is met with, *inter alia*, in cases of under-nourishment, especially combined with a choline deficiency, in cases of severe and protracted physical exertion and wasting illnesses, which is said to be connected with an increased production of suprarenal cortex hormone (general adaptation syndrome). Simultaneously there is an involution of other lymphoid organs also. This incidental thymus involution is reversible like that which appears in the case of X-ray treatment of the thymus. However, it is the reason why, at the majority of autopsies on patients who have died of wasting diseases (apart from leukemia and thyrotoxicosis), the organ is found to be lighter than is normal for the age. The involution takes place rapidly — in three days the organ can lose one-third of its weight (60).

In cases of "status thymicolymphaticus" the thymus is hyperplastic, as is also the lymphoid tissue on the whole. Individuals with this malady or — if it is preferred — constitution, have been considered to have less powers of resistance than have others to all kinds of even inappreciable strains, and therefore inexplicable cases of sudden death have often been assumed to be due to "status thymicolymphaticus." The justification for this conception has been questioned, however, as it has proved that the weight of the thymus in children who have suddenly

lost their lives in accidents does not differ significantly from those in cases of so-called "thymus death." Hypoplasia of the suprarenal cortex is not infrequently met with at the same time as thymus hyperplasia, that is to say a condition of the opposite kind to the "general adaptation syndrome." In such cases sudden death could be ascribed to an insufficiency in the suprarenal cortex, with increased calls on the production of hormone.

The most important primary affections of the thymus are tumours. As has been mentioned above, they are rare, especially during youth (63, 86 a), and often difficult to classify. Dermoid cysts, lipomas, fibromas, myxomas, etc. are of no interest in this connection. Among the thymus tumours proper, "thymomas," Hammar simply distinguishes those that proceed from the epithelial reticulum and those which proceed from the lymphoid elements. EWING (30) divides them according to the same principle into carcinomas, lymphosarcomas and granulomas (Hodgkin's disease), while SYMMERS (83) distinguishes between peritheliomas, epitheliomas, lymphosarcomas, spindle-cell sarcomas and granulomas (Hodgkin). SELYE (76) again mentions, among benign tumours, adenomas and cysts, among malignant tumours, carcinomas, spindle-cell sarcomas and lymphosarcomas. The tumours which have been associated with m.g. have usually been such as contained abundant lymphocytic elements. Congenital carcinomas have been described in a couple of cases (63), but for the rest lymphosarcomas predominate entirely during childhood and youth, although the tumours appear to be most frequent in later middle age. They are approximately twice as frequent in men as in women. In patients under the age of 30 thymus tumours very seldom occur together with m.g. and in childhood practically never.

According to Keynes's above-mentioned collocation (49), thymus tumours are not met with quite so often with m.g. as had been thought earlier (11—12 %). In cases of m.g. without tumours there is no constant divergence from the normal, but histologically it has generally been thought that changes in the thymus were present, although there has been uncertainty as to the specificity. In two cases of m.g. Weise thought he found large

quantities of secretion in the lumina of the primitive bodies, which in his opinion would indicate an increased function of the thymus in cases of m.g. As far as can be judged, however, his results have not been accepted by other research workers. On the other hand, later investigators (78, 17, 19) thought they found "germinal centres" in the thymus in cases of m.g., which is remarkable, since otherwise such centres are seldom met with in that organ. With regard to the reticular epithelium and the Hassall corpuscles, no constant changes have been registered. In general, however, the latter appear to occur more abundantly than in healthy persons.

### Physiology and pathophysiology

*The function of the thymus.* Great uncertainty in the matter of the function of the thymus has always prevailed. Ever since Galenus presumed that the thymus was the seat of courage and affection, more or less loosely founded opinions have been maintained.

Only in the question of the thymus as a lymphopoietic organ is there fairly general unanimity. HAMMAR has also added a poisonbinding function, but with injections of colloidal substances the latter have not been stored up in the reticular epithelium in the same way as in the reticulo-endothelial system. The thymus is considered by many research workers to have a protective effect against infections. HAMMAR (38) associates this function with the fact that, next to the suprarenal cortex, the thymus is the organ of the body which is most abundant in vitamin C. He assumes that the function of the organ is connected with the epithelial cells, and ascribes to the thymocytes a trophic effect on these, possibly assignable to their abundance of vitamin B. The involution of the thymus in the case of infections leads to an increase in the number of Hassall corpuscles, which is said to be due to increased activity with hypertrophy of the epithelial elements. The Hassall corpuscles were not to be looked upon, however, as anything but degenerated remains of epithelial cells without any function of their own. As has been mentioned above, proceeding from his conception of the histophysiology of the gland, WEISE arrived at a similar conclusion. After treatments with extract of thymus, various authors have considered that they found an increase in the antibodies against a certain antigen, and after thymectomy on experimental animals, a decrease in the content of antibodies (12).

Naturally many research workers have tried to prove an endocrine function of the thymus. The resemblance of the gland



to the endocrinous organs speaks in favour of the possibility of such a function, and WEISE even considers that he has proved that there is one. The difference in size at different ages has given rise to an assumption that the thymus probably has something to do with growth, but large series of experiments on animals by various research workers have given contradictory results (60, 28, 25, 44, 71, 57, 75). For the rest an association has been assumed between the thymus and changes in the skeletal structure, the circulation organs, the blood picture, the formation of egg-shell in birds, etc., but up to the present these theories also have not been confirmed (76, 44, 42).

While earlier researchers usually looked for water- or alcohol-soluble thymus hormone, BOMSKOV (13) considers that he found a lipid-soluble hormone, which reduced the glycogen content of the liver, heart, etc., promoted growth, checked the maturing of the sex glands and on the whole contributed towards giving the organism infantile qualities. The lowered glycogen content was said to explain the susceptibility to infections in young individuals and also the so-called "thymus death," which was supposed to be simply a heart death due to too small deposits of glycogen in the myocardium, when a relatively inconsiderable increase in the strain of the heart led to a fatal issue (e.g. narcosis). By measuring the effect on liver glycogen, Bomskov even considers that he was able to titrate out the content of the hormone in different tissues. Thus in the blood it was said to be concentrated in the leukocyte fraction, which agrees very well with Bomskov's theory that the thymus hormone is produced in the reticular cells and transported by the lymphocytes via the blood to all parts of the body. Other researchers do not appear to have been able to confirm Bomskov's results, and these have attracted only inconsiderable attention (are mentioned only in passing in Selye's exhaustive "Textbook of Endocrinology"). The good results which LERICHE and JUNG (52) obtained by means of thymectomy on a 17-year-old girl with arrested growth, general asthenia and infantilism, possibly constitute a certain support for his views.

The disturbance in the metabolism of carbohydrates which goes under the name of v. Gierkes disease or glycogenosis (45), and which is

due to an incapacity in the organism to mobilize stored-up glycogen, ought to be appropriately treated with Bomskov's thymus hormone. CHIEFFI and NASSI (20) have tested a lipoid-soluble thymus extract in cases of this disease and state that they have really obtained favourable effects in respect of certain of its symptoms.

*The thymus and other endocrinous organs.* Experimentally the thymus has proved to be closely dependent on a number of endocrinous organs, something which possibly supports the assumption that the thymus, too has an endocrinous function (76). Thus it has been observed that age involution is prevented by means of adrenalectomy but sets in if suprarenal cortex hormone is injected into the adrenalectomized animal. Other steroids also, e.g. sex hormones, bring about this effect. On the other hand, no lasting effect on the thymus has been seen after hypophysectomy. Probably no special thymotropic hormone exists. The effect which is obtained by means of anterior lobe extract may have come via the sex glands (54) and suprarenal cortex. In about 70 % of cases of thyrotoxicosis enlargement of the thymus is said to be met with. This can be developed experimentally by means of large doses of thyrotropic hormone or thyroidea hormone.

Endeavours have been made to prove a possible thymus function experimentally by studying the effect of thymectomy on young rats. As this is a technically difficult and hazardous operative measure, large doses of X-ray irradiation of the thymus have often been employed, after which the thymus has regressed so violently that it has not been possible to prove any normal thymus tissue histologically. After such treatment certain authors (77) consider they have found regressive changes in the hypophysis and testes, but these results have not been verified by others (42, 44). After thymectomy on dogs Adler found intestinal invagination in several cases, which he interpreted as an effect of the disappearance of the thymus hormone, with the accompanying accumulation of parasymphathetic substances in the blood and tissues.

### Theoretic and experimental aspects of myasthenia gravis and the thymus

In order to study the possible rôle of the thymus in cases of m.g. more closely, it is necessary to dwell a little on the physiological pre-conditions for this disease.

There is general agreement that the muscular weakness which dominates the morbid picture in m.g. cannot be explained on the grounds of chemical or morphologic changes in the central nervous system or in the peripheral nerves, nor on the grounds of such changes in the musculature. In all probability it is due to a block in the transition between nerve and muscle. Thanks to the investigations of Loewi, Dale and Feldberg, it is known that acetylcholine is necessary for the transmission of an impulse from a neuron to a muscle. The acetylcholine is synthesized under the influence of an enzyme, cholinacetylase, and inactivated by another enzyme, cholinesterase. According to NACHMANSOHN (62) these processes constitute links in a chain of extremely rapid reactions, the "acetylcholine cycle," and when this has been elucidated more in detail, it is possible that fresh light will be thrown on the mechanism in m.g. also. Investigations already published would indicate that the muscular weakness is not due to an increased breaking down of acetylcholine effected by cholinesterase (79, 85), but this seems to be synthesized more slowly and in smaller quantities than in healthy individuals (31, 85).

It is of great interest that this incapacity to synthesize acetylcholine in sufficient quantities appears to be associated with a substance circulating in blood serum. Thus, serum from patients injected into dogs has given rise to myasthenic symptoms (1), and it has also been shown objectively to check the contractions in ordinary nerve muscle specimens from frogs (79) although some investigators have been unable to repeat the last-mentioned experiment (18 a). In some cases congenital typical myasthenia has been observed in children of mothers with m.g. (67 a, 79, 80). The symptoms have disappeared after about 14 days and have been explained on the assumption of a blocking factor which has passed from mother to child by way of the placenta. Un-

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fortunately the chemical nature of the blocking substance has not yet been successfully established. According to STONER & WILSON (79) it seems to be an alcohol-soluble instable compound (inactivated after 24 hours in a refrigerator).

Among other experimental investigations it may be mentioned that, in determinations of the synthesis of acetylcholine in the cerebral substance, TRETHEWIE & WRIGHT (86) found a clear increase thereof after the addition of extract of thymus from the newborn, while extract of thymus from m.g. patients led to a still more marked decrease. CONSTANT *et al.* (22 a) have proved an appreciable weakening in the muscular contractions after the injection of water-soluble extract of both normal thymus and thymus from m.g. patients, removed at operations or post mortem. Extract obtained in the same way from the spleen gave somewhat increased muscular contractions. ADLER (1) observed that, after the implantation of puppy or calf thymus, grown dogs developed myasthenic symptoms, as also after the injection of thymus extract free of albumin. BOMSKOV (14) was not able to verify the results of Adler's investigations. Remarkably enough earlier research workers (61, 84) were able to register increased performance capacity in tired muscles with thymus extract obtained according to the same principles as Adler's.

Owing to the connection adduced above between the thymus and m.g., the question has naturally been posed whether under certain circumstances the thymus secretes a "hormone" with effect resembling that of curare. Experiments by MARY WALKER (48, 79, 90) have been adduced against this assumption: With a blood pressure cuff the blood circulation in the upper arms of an m.g. patient is completely inhibited. After 4 minutes' work with the musculature of the lower arm the compression is released. With a short latency period (10 secs. to 4 mins.) clearly increased muscular weakness in other parts of the body also can be observed, e.g. in the form of ptosis. From this Walker concluded that a chemical substance was released in working myasthenic muscles, and via the blood this substance gives rise to a neuromuscular block. Another explanation is that an unusually great shortage of acetylcholine, or one of the preliminary stages of the latter,

appears in the working groups of muscles without normal circulation. When the blood circulation is suddenly restored, a rapid levelling out between the arms and body takes place, which results in a deteriorated supply of acetylcholine even in the groups of muscles which are known from experience to be most sensitive, and which exhibit weakness earliest in cases of m.g., for example *musculus levator palpebræ*. Thus, this experiment should not be incompatible with the thymus theory.

The circumstance that not all patients with m.g. recover after thymectomy has also been adduced against the thymus theory. This can often enough be explained by finds of aberrant thymus tissue outside the operation area, but such finds have not been possible to prove in all autopsies on m.g. patients who had died of exacerbations of the disease some time after the operation. Nor has any agreement between the weight of the thymus and the severity of the disease been found when no tumours were present.

If the possibility that m.g. is due exclusively to changes in the thymus is disregarded, a connection with one of the incretory organs by which the thymus is most influenced may be conceived. In that case it is remarkable that both enlargement of the thymus and myasthenic symptoms have been observed in cases of Basedow's disease and of Addison's disease (22, 82, 49 (88)). For the rest, the first-mentioned disease is not infrequently combined with actual m.g. BOMSKOV (14) maintains that enlargement of the thymus in cases of hyperthyroidism is purely compensatory, i.e. the thymus attempts to counteract the increased activity of the thyroidea. Bomskov has not succeeded in developing myasthenic symptoms with his thymus hormone. He considers that m.g. is due to a dysfunction of the suprarenal cortex, which is prejudicially influenced by processes in an enlarged or tumourous thymus (possibly by the effect of toxic disintegration products). In this connection attention may be called to the hypoplasia of the suprarenal capsules often observed in autopsies on m.g. patients. As in cases of chronic polyarthritis, a remission is not infrequently seen during pregnancy (95), a fact that may also speak in favour of a shortage of suprarenal cortex hormone ("compound E"?) constituting an essential factor in the appearance of m.g. In that

case one ought perhaps to find an accumulation of m.g. among patients with chronic polyarthritis, but as far as I know nothing of that kind has been observed.

The changes which, in cases of m.g., have thus been found in a number of organs with internal secretions, have been interpreted by certain authors as evidence that the disease is, or may be, of diencephalic origin, with disturbance of the endocrinous-vegetative functions (BRAAT (16)). In some cases microscopic changes in the central nervous system resembling those in encephalitis have been proved (GRÖNBERG & STENSTRÖM (34), MEREDITH (58), AUSTREGESILLO (5) etc.). It has also been thought that an increased frequency of m.g. after encephalitis epidemics has been noticed (GRINKER (33)), and in one case encephalitis appeared after the small-pox vaccination of a child with a remission of m.g. (GRÖNLUND (35)).

### The clinical picture of myasthenia gravis

*Occurrence.* M.g. is decidedly most usual in adults, with the greatest frequency at ages between 20 and 30 years and between 40 and 60 years. On the whole it is equally common in both the sexes, but according to observations at the Mayo Clinic (21), at ages above 40 years it is twice as common in men as in women, while at the younger ages the conditions are reversed. There is no definite racial disposition, and cases have been described from all climatic zones. In some cases the disease has appeared in several members of the same family (40, 72, 56), but it is also said to have been observed in only one of two unioval twins (79).

In childhood m.g. is very unusual. LEVETHAN et al. (53) assembled in the literature only eight patients under 10 years of age, of whom no further particulars were given. They appear to have been distributed about equally over the two sexes. With their case, that of a nine-year-old girl, and cases of m.g. in children under 10 years described later, the number has now risen to at least 24 (55, 90 a, 99, 99 a, 100). KAWAICHI & ITO's case was that of a 21-months-old boy of East Asiatic origin and is said to be the youngest among the cases hitherto published. However, in 1940 GRÖNLUND (35) described m.g. in a girl in whom the

symptoms appeared already at 20 months, but this case does not appear to be included in Levethan's series. WALSH (1949) has the largest series of patients under 10 years, i.e. seven cases, 6 of which were negro girls and one a white boy.

GRIFFITH (32) described a morbid picture suspiciously resembling m.g. in a 4  $\frac{1}{2}$ -year-old boy with thymoma, but unfortunately the diagnosis was not confirmed in this case, which speedily had a fatal issue. LEVIN (1949) published two cases of m.g. in siblings with symptoms ever since the foetal life, persisting during the childhood (53 a).

*Symptomatology.* The first symptoms usually have an insidious onset, often during the course of several months, even years. Usually weakness is then observed in the external eye muscles (ptosis or diplopia), less frequently in the masticatory, pharyngeal and laryngeal musculature, or in the extremities. As a rule the disease is fully developed after 1  $\frac{1}{2}$ —6 months. The sick person is troubled by extreme weakness and fatigue, especially in the muscles which are innervated by the cranial nerves, but also in the trunk and extremities. As regards the latter, it is often found that the fatigue is greater proximally than distally. It increases rapidly with movement. When the pharyngeal musculature is involved, the intake of nourishment is made more difficult, which leads to inanition and may be attended by a risk of aspiration of food. Especially dramatic are the cases where the respiration musculature is attacked, which sometimes occurs very rapidly with an impending risk of suffocation. ASK-UPMARK (3, 4) has studied cardiac changes in cases of m.g. and points to the usual occurrence of tachycardia, dyspnoea, spontaneous or in connection with slight exertions, and occasionally of precordial pains with corresponding eeg. changes (lowered ST, "pathologic" T-waves). The heart symptoms should be ascribed chiefly to the reduced venous return flow to the heart due to the myasthenic change in the skeletal musculature, in the second place to changes in the myocardium itself (at autopsies round cell infiltration even in the musculature of the heart has been found in several cases). Ask-Upmark thinks it probable that m.g. can occur isolated in the myocardium, as also in other groups of muscles.

At the examination normal sensitivity, usually no, or only inconsiderable, muscular atrophy, normal or, in cases of extreme fatigue somewhat weakened, musculature reflexes are found. The abdominal reflexes and plantar reflexes normal. The pupillary reflexes usually normal but some times slow or easily tired. Accommodation paresis has been described. The facial musculature is nearly always involved, which results in a characteristic expressionless "facies myasthenica." Disturbances in



speech are often striking. The speech becomes low-pitched, toneless, slurred, especially when the sufferer is tired, e.g. when he has to read aloud or count aloud to 50. If the soft palate is paretic the speech has a nasal sound.

*Course.* The course of the illness, especially in untreated cases, is very varied. Sometimes strongly localized symptoms have been observed, e.g. a unilateral ptosis, approximately constant for months and years, but in the majority of cases more or less rapid progress and dispersion of the symptoms are seen, possibly interrupted by remissions of different degrees and duration. Such remissions are most usually met with in young individuals with relatively short anamneses. In 87 patients who had not been treated with prostigmin KENNEDY & MOERSCH (47) saw remissions in 27 cases, lasting on an average 2.2 years with extreme limits of 1/12 and 16 years. Subsequently, among 125 cases treated with prostigmin, HARVEY (41) found only 17 remissions, but 9 of which lasted more than 2 years and only one over 5 years. Thus it appears as though prostigmin treatment counteracts the spontaneous tendency towards remissions of the disease.

In untreated cases myasthenia gravis usually persists over several years and even decades, during which, as a rule, the sufferer is greatly invalidized, condemned to lead a life without physical exertions. In addition there is always a risk of an acute exacerbation, which may have a fatal issue. An otherwise quite commonplace infection of the respiratory passages can give rise to a deterioration of this kind. Cold, even moderate cold, leads to a disagreeable sensation of stiffness in the musculature and incapacity for active movements. Warmth, particularly direct sun irradiation during the summer, is said to be still worse, however, and may possibly lead to a collapse which threatens to be fatal. Tolerance to surgical and other physical measures is often very much reduced, even enemas have led to shock-like conditions (49) difficult to overcome. Further, in a number of cases a definite connection has been observed between mental excitement and exacerbations, and the question has even been posed whether so-called psychic traumata could give rise to the disease. As a rule, during menstruation a deterioration is seen, in contrast to the state of things in pregnancy, which usually leads to a remission. Thus, in itself, m.g. is *not* an indication for abortion (96).

Among pharmaceutics quinine and curare have proved to lead to greatly intensified symptoms, the latter already with a



dose of 1/10 to 1/40 of that which in healthy individuals gives a slight curare effect. Thus, m.g. constitutes a decided contraindication against the use of curare in connection with operative measures.

**Diagnosis.** If attention is centred on this disease, the diagnosis m.g. is usually easy to make with the guidance of the anamnesis and the examination findings. There are, however, cases with atypical courses or greatly restricted localization, where the diagnosis may present difficulties. Many m.g. patients have certainly been classed as cerebral tumours, sclerosis disseminata, amyotrophic lateral sclerosis, encephalitis, neurosis, hysteria or something of that sort. Since WALKER's discovery of the diagnostic value of prostigmin the possibilities of arriving at a sure diagnosis have been enormously increased. VIETS & SCHWAB have worked out a special prostigmin test (94) based on the subjective and objective improvement of the patient during one hour after the injection of 1.5 mg of prostigmin. These observations are noted every tenth minute, the improvement observed being graded from 0 to 4 (0 = no improvement, 1 = slight, 2 = moderate, 3 = considerable and 4 = complete restitution). The points are added up after 1 hour, as shown in the following example:

	Objective	Subjective
	improvement	
10 mins.....	1	2
20 mins.....	3	4
30 mins.....	4	4
40 mins.....	4	4
50 mins.....	2	4
60 mins.....	2	3
	16	+ 21 = 37.

If the total is above 18 the test is regarded as positive, if it is lower than 8 it is negative. If between values are obtained, the test should be repeated. In the majority of cases, however, the effects with prostigmin will probably be so striking that this second test is seldom necessary.

When the deglutition mechanism is affected, its state can be studied by means of screening before and after prostigmin injections. Retention of a swallowed contrast in the pharynx and piriform sinus is proof of an organically conditioned affection. A prostigmin injection leads to an appreciable improvement, which is pathognomonic of myasthenia gravis (74).

Taking the abnormal sensitivity to curare of m.g. patients as a starting point, BENNETT & CASH (7) worked out another method of investigation. During the course of one minute 0.1 mg of curare/kg of body weight is injected intravenously (= 1/10 of the dose which gives rise to

a faint curare effect in healthy persons). If m.g. is present, within two minutes aggravation of the existing myasthenic symptoms is then seen, and fresh ones may appear, even a threatening fatal deterioration. Therefore, the experiment must be concluded within 2 to 3 minutes, with an intravenous injection of 1.5 mg of prostigmin. All symptoms conditioned by curare and m.g. then disappear within a minute. As this test involves certain risks, and the diagnosis can usually be made with prostigmin only, it will probably only be necessary to use curare as a diagnostic in unusual cases of m.g. localized mainly in the musculature of the extremities.

Faradic current, which gives a tetanic contraction of the stimulated muscle in healthy persons, gives a very transient contraction in cases of m.g. ("Jolly's reaction," "myasthenic reaction"), which is often important for the diagnosis, but which is also met with in other morbid conditions, such as hyperthyreosis and Addison's disease.

Electromyography (87) will hitherto have been of little diagnostic value in practice, although it shows typical changes in cases of m.g., clearly illustrating the successive lengthening of the recovery phase with repeated contractions and the restoration of normal muscular action by means of prostigmin.

The effect of intra-arterial injections of prostigmin (10) is of more theoretic than practical value. While the injection of 0.5 mg in art. brachialis in healthy individuals leads to a weakening of the strength of the hand and fibrillations, after 1.5 to 3 mg intraarterially an appreciable improvement in the strength of the hand without secondary effects results in the majority of m.g. patients.

Laboratory investigations are of but little value. In many cases increased amounts of creatine in relation to creatine are met with in the urine, which is said to be due to the inconsiderable muscular activity. This finding will hardly be of any diagnostic importance.

*Medication therapy.* Nowadays the therapy is dominated by prostigmin treatment, which has rendered it possible for patients to lead a far more normal existence than before 1935. The dose varies greatly, all depending on the severity of the case. VIETS (96) indicates the limits  $2 \times 7.5$  mg and  $25 \times 15$  mg with an average of  $10.9 \times 15$  mg. In severer cases the dose must be given in the form of injections, either alone or combined with peroral treatment. Thus only after an injection have certain patients been able to eat a proper meal to keep up their weight. Viets also recommends that every myasthenia gravis patient should be provided with an injection syringe and ampules of prostigmin for

immediate use in the event of respiration paresis. The effect of prostigmin endures for 6—8 hours.

Prostigmin is not a remedy proper. Its use and importance in cases of myasthenia gravis can be best compared with those of insulin in diabetes. It has been assumed that it temporarily inactivates the cholinesterase and thereby prevents the splitting up of the acetylcholine. According to STONER & WILSON (79, 97), this assumption does not constitute a sufficient explanation, but they find it possible that the prostigmin also has a neutralising effect direct on the previously-mentioned curare-like substance in the blood serum. The prostigmin is often combined with atropine to reduce the muscarine-like effect on smooth musculature (salivation, sweating, increased peristalsis, etc.).

In place of atropine ephedrine may be used, which also in itself has proved in a number of cases to lead to an evident improvement, and was largely used before the emergence of prostigmin (26, 65). In combination with prostigmin ephedrine has both a potentizing and a protracting influence on the effect of prostigmin (97). According to VIETS (96) it is appreciated by about 50 per cent of the patients. The dose is  $25 \text{ mg} \times 2-3$ , preferably not in the evening (risk of sleeplessness).

With a comparatively small number of patients potassium-chloride proves to lead to an improvement when given alone or together with prostigmin, but owing to its repulsive taste and the large quantities which are necessary ( $4 \text{ to } 6 \text{ g} \times 6$ ) it is seldom used, at least not over considerable periods. Its effect may conceivably be connected with the reduction proved by CUMINGS (23) in the potassium content in the blood serum of persons with myasthenia gravis. On the other hand, in the latter potassium is found in considerable quantities in the musculature. In prostigmin treatment the potassium balance is corrected by the passage of potassium from the muscles to the blood serum. Good results are said to have been obtained also by the administration of large amounts of glycocoll (30 g/day), and this has been attributed to the metabolism of creatine by the muscles.

The medicament which, along with prostigmin, has proved most valuable, however, is guanidine hydrochloride, which, like glycocoll, will probably have some connection with the metabolism in the muscles. (Glycocoll + guanidine  $\rightarrow$  creatine). Accord-

ing to MINOT (59), the suitable dosage is 10—30 mg/kg of body weight. Overdosage often results — especially during the first period — in such severe paresthesias in the finger-tips, round the mouth or in the urinary bladder (cystic symptoms in spite of sterile urine) that the medication has to be interrupted (24). There are patients, however, who are completely free of trouble with guanidine hydrochloride alone (96).

It is stated that in individual cases improvements and even freedom from symptoms have appeared after treatment for some time with vitamin B<sub>1</sub> (spontaneous remission?) (5).

In very recent years a number of cholinesterase-antagonists with a more lasting effect than prostigmin have been tested, e.g. di-isopropyl-fluorophosphate (DFP), hexa-ethyl-tetraphosphate (HETP) and tetra-ethyl-pyrophosphate (TEPP). The last-named seems to be the most useful. Its secondary effects are of the same nature as with DFP and HETP, but the dose is easier to regulate, the compound is more stable, and it can be given per os. BURGEN et al. (18) consider that TEPP can replace prostigmin. It is certainly only 1/3—1/2 as effective as the latter, but its effect lasts twice as long, and it has more cumulative properties. If TEPP is given in smaller doses than are required to secure the maximum effect, an appreciable potentialisation of the effect of the subsequent supplies of prostigmin sets in. Thus a combination of TEPP and prostigmin per os would be an improvement in the treatment of m.g., especially in the cases where large amounts of prostigmin are otherwise necessary. Toxic symptoms are common, however, with TEPP also, and they cannot all be excluded with atropine.

Attempts at treating the disease with the substances which are now so much to the fore, "compound E" and ACTH are said to have been made with promising results (101), as might theoretically be expected, in view of the connection referred to above between m.g. and the function of the suprarenal cortex. No detailed report on the matter has yet been given.

*Thymectomy.* The above-discussed connection between the thymus and m.g. has led to attempts to effect an improvement by means of operative measures on the thymus, in the first place when an enlargement of the thymus has been diagnosed clinically, but even when one cannot be proved. SAUERBRUCH performed the first thymectomy (published 1912) on a 20-year-old girl with thyrotoxicosis and myasthenia gravis (9). The last-mentioned disease exhibited successive regression after the operation, and the thyrotoxicosis was favourably affected by strumectomy a year later. A pathologic-anatomic examination of the thymus revealed hyperplasia of the infantile type (weight 49 g). According to ADLER (1),

von Haberer has subsequently described some cases of m.g., the majority with thyrotoxicosis also, where strumectomy and thymectomy led to satisfactory improvements. ADLER (1) (1938) describes two cases of m.g. in which thymectomy was performed at Sauerbruch's clinic. In one case there was a benign, lymphoepithelial tumour. This patient, a 39-year-old woman, who had had symptoms for 5 years, showed an improvement the first few days after the operation but died on the eighth day of mediastinitis and pleural empyema. The second case was that of a 24-year-old woman who had had m.g. for  $2\frac{1}{2}$  years. At the operation only the right lobe of the thymus could be found and removed. Even the same day an obvious improvement set in, and the requirements of prostigmin were subsequently considerably less than before the operation.

The first successful operation on a thymus tumour as a complication of m.g. was described in 1939 by BLALOCK et al. (11). A cystic tumour was removed from a 19-year-old girl, who had had severe myasthenic symptoms for 4 years and large daily doses of prostigmin. One year after the operation, she was quite well, and according to later information was still free of trouble 4 years after the operation (9).

Since these pioneer works, a large number of more or less successful thymectomies have been published (8, 9, 50, 64, 69, 73, 94). As early as 1941 BOMAN, from Crafoord's clinic, described two operated cases of thymoma with m.g. In one case a cystic thymoma the size of a walnut was removed from the bifurcation of art. carotis communis on a 73-year-old woman, but the operation had no effect on the myasthenic symptoms, and the patient died three weeks after the operation of granulocytopenia and pulmonary atelectases. The second patient, a 31-year-old woman, became entirely free of symptoms after the operation.

Considerable collocations have been made, *inter alia*, by CLAGETT & EATON (21) at the Mayo Clinic comprising 32 operated cases, two of the patients having died on the third day after the operation and two after three and six months respectively. In 9 cases no improvement, or only an inconsiderable improvement, was observed. The other 19 cases exhibited obvious improvement, 3 even complete remission. In many cases the improvement did not set in until six—nine months after the operation. In 1945 KEYNES (48) described 63 thymectomies in cases of m.g. In a later collocation (1949) (49) the figure had risen to 155. Keynes considers that the prognosis is less favourable in cases with thymomas, in contradistinction to Clagett & Eaton, who found in their material at least as good results in tumour cases as in others. For the time being, therefore, he ignores the 18 tumour cases when judging the results of thymectomy in cases of m.g. Ten patients died after the operation (of whom seven among the first 21 cases), and in seven cases there were not sufficiently long observation periods. Of the other 120 patients,

79 exhibited complete, or almost complete, remissions. A further 31 were somewhat improved, but in ten there was no improvement at all. Keynes, like Blalock, considers that the effect is best with young patients with short anamneses.

It is of interest that Keynes's series includes two children, girls of 4 and  $2\frac{1}{2}$  years of age respectively. Both were in poor condition before the operation. Before treatment with prostigmin was begun, they had had to be tube-fed and treated with respirators. The operations revealed histologically normal thymus glands weighing 17 g and 5.5 g respectively. After thymectomy, the dose of prostigmin could soon be reduced from 60 mg to 5 mg for the older child, and from 80 mg to 25 mg for the younger. The latter died 4 months after the operation in an acute exacerbation. At the necropsy one thymus lobe was found to be untouched. Four years after the operation the older girl is still free from trouble (99 a).

In the individual case it is important to know the indications for thymectomy, but in this matter there appear to be divergent opinions. While NELLEN (64) advises operations in every case of m.g., Blalock and Keynes say nothing about indications but emphasize the more favourable effect of operations on young patients with short morbid histories. However, Keynes has observed surprisingly good results also in patients with long anamneses, but then not until after long observation periods. VIETS (96) question whether a spontaneous remission sets in after the operation and thus whether thymectomy in itself explains the effect of the operation. Like WYLLIE (99 a) he considers that operations should not be performed on patients who can get along with moderate doses of prostigmin, nor on persons over 50 years of age. LAURENT (48) (1945) takes up an entirely negative attitude towards the operation and points out — as do, *inter alia*, VIETS and HAFSTRÖM (37) — that, when the results of the operation are judged, the tendency of the disease towards spontaneous remissions must be taken into account. Keynes's latest collocation, however, with about 65 per cent of entirely or practically entirely, recovered patients speaks decidedly in favour of the operation being justified on fairly wide indications, possibly with some reservation for cases with thymomas. In consideration of the nature of the measure the operation mortality is amazingly low.

*X-ray treatment.* As has been mentioned previously, a total atrophy of the thymus has been successfully effected on animals by means of strong X-ray irradiation. It has, then, seemed natural in cases of m.g.

to try to obtain a favourable effect by means of X-ray irradiation of the thymus. A number of authors (48) consider that in some cases they have found an improvement from X-ray treatment, in other cases no effect at all. POER even states that he, like ARONSON (2, 69), has observed a clear deterioration after irradiation of the thymus. There are, therefore, different views about the value of this form of treatment. In any case it is certainly less favourable than thymectomy. It may possibly be indicated as a pre-operative treatment in the case of tumours in the thymus.

### The author's own case

Girl, born on 18/5 1939. The eldest of three children. Brother, born 1947, has congenital bilateral club-foot. For the rest no hereditary somatic or psychic affections in the family.

Weight at birth 3 330 g. The delivery and the development during the year of infancy normal, apart from whooping-cough at the age of 7 mos. Up to the year 1946 protracted bronchitis in the spring and autumn. In 1941 rubeola, 1943 measles and varicellae, 1944 parotitis. No complications of the epidemic diseases. Psychically she appeared to be a perfectly normal child, did well at school and had no difficulty in getting on with her parents and friends.

In August 1948 gradually increasing fatigue, first appearing in the eyes, and soon also in the extremities after exertion, e.g. walking upstairs. Appeared pre-occupied, as if uninterested in her surroundings. Learned her homework as well as previously, however. The parents suspected that the girl had auditory hallucinations. Appetite poor. At a medical examination on 16/11 1948 poliomyelitis was suspected, and, therefore, the patient was admitted to the infectious diseases hospital, where, however, the possibility of that illness could be precluded. During this period at the hospital her condition deteriorated, her mouth was always open, she dribbled and had difficulty in swallowing, which was apprehended as a refusal to take nourishment (schizoid psychopathy?). Psychiatrists were consulted on 26/11. A certificate was issued, as, owing to the refusal to take food, the patient's life was considered in danger. While waiting for a suitable place in a mental hospital, she was admitted to the Children's Department here on 30/11 1948.

Status when admitted (Fig. 1). Fairly small for her age, very emaciated (height 139 cm, weight 25.0 kg). Pale. Musculature feebly developed in general. No incompensation symptoms from cor. Hanging lower jaw. Appears anxious, negativistic and repressed. Answers only in monosyllables, in a low voice, slurred, or not at all. Dragging, swaying gait. Skin and internal organs normal. General hypotonia and reduction of the physical strength; in particular the facial and masticatory musculature appear to be affected. Slow contraction of pupils bilat. with incident light, other reflexes normal. Fundi oculi normal. (Elam).



Fig. 1. The patient at the time of admission (1/12 1948).



Fig. 2. The patient  $2\frac{1}{4}$  months after thymectomy.

Laboratory findings: Urine and blood values without special remark (the creatine content in the urine not determined, however). Series determinations of blood sugar: Low values (varying between 0.068 and 0.120 per cent during 24 hours). Glucose loading: Fasting value 0.040 per cent. After 30 mins. 0.095 per cent, followed by successive reduction to 0.058 per cent after 4 hours. Basal metabolism rate:  $-10$  per cent. Wassermann reaction in blood neg.

X-ray examinations: Lungs and mediastinum normal. Sella turcica normal.

Stimulation with galvanic current: Normal contractions. With faradic current typical myasthenic reaction.

For diagnostic purposes on 2/12 1948 the patient was given 0.5 mg of neostigmin (i.e. prostigmin) subcutaneously. Within 30 to 45 mins. a striking change in her reactions and behaviour set in:



*Before the injection.*

Apathetic, tired, listless, resists examination. Ptosis bilat. Lower jaw hangs open. No spontaneous speech.

Can swallow about one gulp. Has not strength to chew at all.

Speech difficult to understand. Very weak, indistinct and inarticulate phonation.

Cannot read more than about 3/4 of a line in a child's reader and then becomes very tired.

Pupillary reaction to light slow.

*After the injection.*

Gay. Behaves like a normal child. Walks about and talks to the staff and fellow-patients. No ptosis. Mouth closed. Less negativistic to examinations.

Eats bread and butter, etc. with a good appetite.

Speech clear and distinct, even in the case of difficult consonants.

Even after reading a whole page aloud no signs of being tired.

Pupillary reaction normal.

A clear increase in the performance capacity in the extremities also could be registered.

As the diagnosis m.g. could thus be considered definite, the patient was placed on neostigmin per os, 15 mg  $\times$  6, and ephedrine 0.25 mg  $\times$  2, the latter as it gave her an obvious subjective improvement. During ambulant observation the dose of neostigmin had to be increased to 15 mg  $\times$  7. With that dose she was subjectively and objectively free of trouble, possibly with the exception of a slight persisting ptosis of the eyelids. Got on well at school again without difficulty. During observation period in the Children's Department in May, 1949, her minimum requirements of neostigmin were found to be 15 mg  $\times$  4 when resting and 15 mg  $\times$  6 to 7 when up and about.

In view of the good results of thymectomy described in the literature, especially in young people with short anamneses, this operation was considered motivated in this case, which showed no tendency whatever towards remission. After consultations with Prof. Crafoord, the patient was therefore admitted to Sabbatsberg Hospital. 3/6 1949. Op. (Crafoord) *Thymectomy*. Incision in the median line from the upper edge of manubrium sterni down to immediately above the processus xiphoideus. 2/3 of the length of the sternum was slit with a Schumacher scissors from the jugulum downwards. The two halves were carefully separated. Then we cut into the anterior mediastinum and freed the whole of the somewhat voluminous thymus, which as usual consisted of two longitudinal lobes, an isthmus part and two horns directed cranially. The main vessel supply was situated in the hilus area, within which an artery the thickness of a knitting-needle ran into the thymus. This artery emerged from the right of the throat, and it could not be said with certainty where it came from. From the same area ran two short veins, which after a bare 1 cm course opened into vena anonyma sin. These vessels were doubly

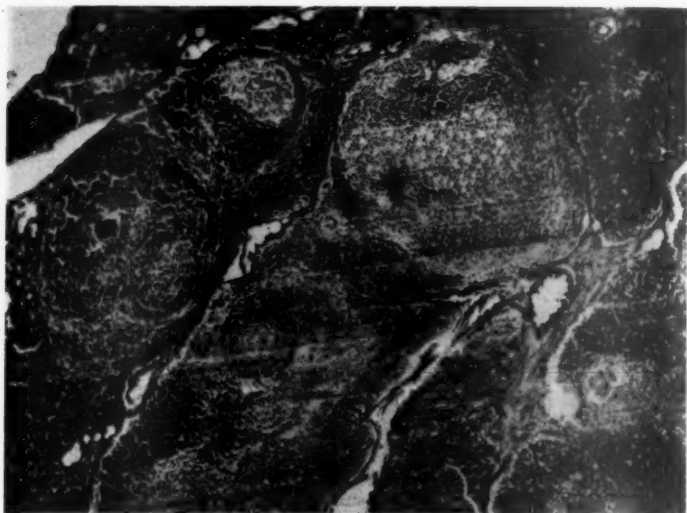


Fig. 3. Stained section of the extirpated thymus. Note the numerous germinal centres.

bound and ligatured. Some small vascular connection with the mediastinal connective tissue were held with a Pean's clamp and ligatured during the excision of the thymus. It was on the right side on a small area, fairly firmly attached to the right very thin pleural sac. Here there was a small lesion, which was seized with a Pean's clamp and ligatured. Only an inconsiderable amount of air was sucked in. The sternum was then sewn with two metal sutures.

The extirpated thymus tissue weighed 40–42 g (weighed in fixed condition after a couple of small pieces of tissue had been cut out). The Hassall corpuscles were numerous and of the usual appearance. The thymus contained an abundance of lymphocytes with numerous germinal centres. No changes in the stroma. (Fig. 3.)

The after-course free of complications. During the month immediately after the operation, no reduction in the requirements of neostigmin. Again admitted for control of this on 22/8–3/9 1949 to the Children's Department, Karlstad. Status: Height 142 cm, weight 31.3 kg. Spare build. Slight ptosis. Tachycardia (about 120/1 min.). For the rest nothing of note in the status. During her stay in the hospital the patient was not given any neostigmin tablets. In the afternoon she then had a subjective sensation of fatigue, which did not, however, affect her activ-

ity, but she took part even at that time of day in the games and walks in the park with other patients. Only when she went upstairs quickly could fatigue be objectively established. Electro-cardiogram and X-ray of the heart normal.

In order to get an idea of the possible effect of the disease on the function of the heart, the pulse was counted before and after she had run up and down stairs and with and without neostigmin (1 mg subcutaneously):

Pulse frequency and other observations		
Before injection of neostigmin. 30 mins. later		
Before physical exercise	124/min.	92/min.
Running up and down:	2 flights of stairs	3 flights
Condition after exercise:	Legs very tired	Almost unaffected.
Pulse immediately after exercise:		
	160/min.	144/min.
After $\frac{1}{2}$ min.	120	108
" 1 "	132	100
" $1\frac{1}{2}$ "	128	104
" 2 "	132	108
" $2\frac{1}{2}$ "		108
" 3 "		112
" 5 "		96

About a month later the same experiment was carried out, but with gynergen instead of neostigmin. Then also a decrease in the tachycardia made its appearance, but it was not so marked (from 116 to 104/min. during rest). No certain effect on the performance capacity. Ecg. changes after gynergen and prostigmin tallied on the whole both during rest lying down and standing and after work. Apart from the effect on the frequency, they found expression in that the T-waves, above all in lead III, became more marked.

(Add. to the proof: Examination  $\frac{26}{8}$  1950: Subjectively all well. Since June 1950 no need of neostigmin. Height 149.5 cm, weight 36.9 kg. No ptosis.)

*Discussion.* The case described here is of interest from different points of view, even apart from the age of the patient. It illustrates, *inter alia*, the diagnostic difficulties which may be met with, if one has not the possibility of the presence of this disease in mind. There were at least undeniable criteria for suspicions of schizophrenia.

Further, the patient is one of the youngest patients hitherto operated upon for myasthenia gravis, and already 2—3 months

after thymectomy there was almost complete remission. As Keynes, *inter alios*, pointed out, patients who have improved after the operation are often apt to continue their prostigmin medication, although objectively there is no reason for them to do so; they dare not rely on the improvement being definitive. This was the case with this patient, too, who still five months after the operation wants 1—2 tablets per day "to be on the safe side." Probably she will have an increased feeling of safety in time if the improvement proves to be lasting.

Apart from tachycardia, it was not possible to prove any changes in the heart in this case. As far as can be judged, the tachycardia had extra-cardiac causes, possibly a reduced venous return flow from myasthenic musculature. The rapid fall in pulse frequency after exertion speaks against any myasthenia cordis proper being present.

It is worth mentioning that a guinea-pig test was carried out during the first part of the time the patient was in the hospital, before she had yet been placed on neostigmin. 3 ml of serum from the patient was injected subcutaneously in the thigh of a guinea-pig. Within 10 mins. paresis had set in on both hind legs, which were stretched out backwards when the animal tried to drag itself forward with the help of the fore-legs. On the whole the animal's activity was greatly reduced. The paresis did not begin to pass off until after 6 hours. After 24 hours the animal was apparently quite free of trouble. A control animal was given instead an injection of 3 ml of serum from a nine-year-old girl with gastro-duodenitis and exhibited no symptoms whatever of paresis or anything of that kind. The experiment was repeated after the patient had been under neostigmin treatment for three weeks, and then no difference could be observed between the experimental animal and a control animal.

### Summary

There is a definite connection between the thymus and myasthenia gravis (m.g.), but the nature of this connection is a matter of discussion. In serum from patients with myasthenia gravis there is an element which, injected into other individuals, gives rise to

myasthenic symptoms owing to a neuro-muscular block, which must probably be ascribed to a reduced synthesis of acetylcholine.

The intimate dependence of the thymus on other endocrinous organs renders it probable that myasthenia gravis is also influenced by them, above all by the thyroidea and suprarenal capsules.

In myasthenia gravis remissions are often seen — as in cases of chronic polyarthritis — during pregnancy, a fact which ought to stimulate therapeutic experiments with "compound E" or ACTH. In some cases, too, changes resembling those in encephalitis have been found in the brain.

The disease has been considered rare in children, but with increased diagnostic possibilities ever increasing numbers have been discovered and described. There are now reported between 20 and 30 cases amongst children under 10 years (three cases transient myasthenia in newborn children of mothers with myasthenia gravis are excluded).

After a survey of the clinical picture of the disease, a case in a nine-year-old girl is described, in which it first appeared with a morbid picture suggesting schizophrenia. Following thymectomy about 10 months after the appearance of the first symptoms, there was almost complete recovery.

### Résumé

Il y a un rapport défini entre le thymus et la myasthenia gravis, mais la nature de ce rapport est un sujet de discussion. Dans le sérum de malades atteints de myasthenia gravis, se trouve un élément qui, injecté chez d'autres individus, provoque des symptômes myasthéniques dus à un bloc neuro-musculaire, qui doit probablement être attribué à une réduction de la synthèse d'acétylcholine.

Le fait que le thymus est intimement dépendant des autres organes endocrines rend probable que la myasthenia gravis est aussi influencée par ces derniers, surtout par la thyroïde et les capsules surrénales.

Dans la myasthenia gravis on observe souvent des rémissions — comme dans des cas de polyarthrite chronique — pendant la

grossesse, fait qui devrait stimuler les expériences thérapeutiques avec le "composé E" ou l'ACTH. Dans certains cas aussi on a constaté dans le cerveau des changements ressemblant à ceux de l'encéphalite.

La maladie a été considérée comme rare chez les enfants, mais avec les possibilités croissantes d'établir le diagnostic, on a découvert et décrit un nombre toujours croissant de cas. Entre 20 et 30 cas ont été décrit jusqu'ici chez des enfants de moins de 10 ans. (Trois cas de myasthénie transitoire chez des nouveau-nés dont les mères étaient atteintes de myasthenia gravis sont exclus.)

Après une étude de l'image clinique de la maladie, l'auteur décrit le cas d'une fillette de 9 ans, chez laquelle la maladie a tout d'abord présenté une image morbide suggérant la schizophrénie. Après une thymectomie environ 10 mois après l'apparition du premier symptôme, il y a eu guérison presque complète.

### **Zusammenfassung**

Bestimmte Gründe sprechen für einen noch ungeklärten Zusammenhang zwischen Thymus und Myasthenia gravis (M.g.). Im Serum von Patienten mit M.g. findet man eine Substanz — möglicherweise durch eine reduzierte Synthese von Acetylcholin entstanden — welche anderen Individuen injiziert myasthenische Symptome durch einen neuromuskularen Block hervorruft.

Die nahe Abhängigkeit des Thymus von anderen endokrinen Organen macht es wahrscheinlich, dass M.g. auch von diesen, vor allem der Thyroidea und den Nebennieren, abhängig ist. Bei M.g. sieht man, wie bei kronischer Polyarthrit, oft Remissionen während der Schwangerschaft, weshalb therapeutische Versuche mit "compound E" oder ACTH angebracht erscheinen. In einigen Fällen fand man encephalitisch erscheinende Veränderungen im Gehirn.

M.g., welche früher bei Kindern selten beobachtet wurde, wird mit den jetzt besseren diagnostischen Möglichkeiten immer öfter gefunden. Es sind bis jetzt zwischen 20 und 30 Fälle für Kinder unter 10 Jahren beschrieben worden (drei Fälle von vorübergehender Myasthenie bei Neugeborenen von Müttern mit M.g. sind dabei ausgeschlossen).

Nach einer Schilderung des klinischen Bildes beschreibt Verf. einen Fall eines 9-jährigen Mädchens. Das Krankheitsbild schien im Anfang auf Schizophrenie zu deuten. Nach Thymektomie etwa 10 Monate nach Beginn der Krankheit trat so gut wie vollständige Heilung ein.

### Resumen

Hay una determinada relación entre el timo y la miastenia gravis, pero la naturaleza de esta relación es un caso de discusión. En el suero de enfermos atacados de miastenia gravis se encuentra un elemento que inyectado en otros individuos provoca síntomas miasténicos debidos a un bloque neuromuscular, que debe de ser atribuído a una reducción de la síntesis de acetilcolina.

El hecho de que el timo esté íntimamente dependiente de los otros órganos endocrinos hace probable que la miastenia gravis esté también influenciada por estos últimos, principalmente por la tiroides y las cápsulas suprarrenales.

En la miastenia gravis se observan frecuentemente remisiones — como en los casos de poliartritis crónica — durante el embarazo, hecho que debería estimular las experiencias terapéuticas con el “compuesto E” o el ACTH. En ciertos casos también se han comprobado en el cerebro transformaciones parecidas a las de la encefalitis.

La enfermedad ha sido considerada como rara en los niños, pero con posibilidades crecientes de establecer el diagnóstico se ha descubierto y descrito un número siempre creciente de casos. Hasta ahora se han descrito entre 20 y 30 casos en niños de menos de 10 años (se excluyen tres casos de miastenia transitoria en recién nacidos, cuyas madres estaban atacadas de miastenia gravis).

Después de un estudio de la imagen clínica de la enfermedad, el autor describe el caso de una muchacha de 9 años, en la cual la enfermedad ha presentado primeramente una imagen mórbida indicadora de la esquizofrenia. Después de una timectomía alrededor de 10 meses más tarde de la aparición del primer síntoma ha habido una curación casi completa.

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## Chest Electrodes for Children

by

ELIAS BENGTSSON

Unipolar electrocardiographic chest leads have become an important supplement to the technique of complete cardiac examination. They assume especial importance in cases of congenital defects of the heart, in the diagnosis of disturbances in intraventricular conduction, in myocarditis, and in accurate localization of different positions of the heart.

Examination with chest leads in children may be slow, requiring patience and a special technique. Particular attention must be paid to the choice of electrodes.

The electrodes most commonly used are flat or concave and about 10 mm in diameter. They are usually attached to the skin by adhesive tape or some similar material. A copper wire is soldered directly onto the electrode surface either perpendicularly or tangentially and the intake of the banana plug may be attached directly to the electrode. The contact surface with the skin is generally unsatisfactory, due to the fact that the electrode is too light in comparison with the cable. Satisfactory fixation may be obtained, however, with the use of an EEG electrode attached by collodion in the same way as in EEG registration. This is a very suitable electrode for its purpose, but has certain disadvantages in that it is easily breakable and requires repeated repairing and the collodion fixation is rather time-consuming.

There are several reasons why the sucking electrode is not the one of choice in children. Those with even the smallest diameter are unsuitable, as the contact surface with the skin is too large. Thus electrodes placed in the positions  $V_3$ - $V_5$  are able to register potentials from both the right and left ventricles of the heart;

a more exact registration is impossible. If the diameter of the sucking electrode is made smaller, it will not adhere to the skin.

If a concentric insulating plate is placed around the periphery of the electrode in order to diminish its surface area while maintaining its adhesive capacity, there is a chance that the surface contact with the skin will not be accurately localized. Even with this precaution, sufficient contact may not be obtained. Yet for obvious reasons, the exact localization of chest electrodes is of great importance in children. The sucking electrode has the practical advantage of being easily and quickly applied. However, daily care, particularly with respect to thorough cleaning, is necessary lest the contact surfaces become unsatisfactory and produce technical disturbances in registration, simultaneously losing their adhesive capacity and detaching easily. The flat electrode surface does not adhere as easily to the surface in children as in adults, due to the fact that the child's chest is more convex. During ECG registration in children, which is in itself time-consuming, it is often necessary to re-apply loosened electrodes, a procedure which disturbs not only the examiner but also the child. The pinch of the sucking electrode on the skin is often an obvious cause of pain in infants and small children.

The Elema Company has kindly placed a new type of precordial electrode of German make at the disposal of the author. This consists of five ordinary electrodes joined together by movable arms which can be shifted in different directions. These are attached to a band of cloth stretched around the thorax. This arrangement allows movement of the electrodes beneath the band to the desired locality. It is difficult, however, to obtain good fixation in position, as the electrodes slide easily and cannot be applied quickly.

When several precordial leads have to be taken daily, or when they are taken by technical assistants, it is necessary to have a technique which takes as short a time as possible but at the same time gives sufficient precision.

In order to fulfill these criteria, the author devised the following simple but useful technique, which he has employed in more than 200 cases.

The electrode consists of an ordinary copper rivet. The convex surface is polished and the contact surface completely silvered. A surface diameter of 7 mm was arbitrarily chosen for children under 7 years and of 8 mm for children over 7 years. On the rivet a thin copper lead, consisting of many fine threads, is soldered. The distance from the contact surface of the electrode to the rubber insulation of the lead wire is thoroughly insulated. In order to fit the electrodes on the thorax, a band of rubber 40 cm long and 12 cm wide is used. This band is perforated with round holes 3 mm in diameter and as close to one another as possible through which the heads of the rivets are placed. To each end of the band is sewed a broad piece of cloth which can be tightly fastened with eyes and regulated in length as close as one cm for different sizes of the thorax.

The strength of the material and its extent, covering the entire thorax from the axilla to below the costal margin, makes this device steady, but not unpleasant. The respiratory excursion of the thorax is diminished only slightly. The only disadvantage of any importance is that slight displacement of the points marked on the skin for localization of the electrodes is conceivable, due to the size and amount of the patient's subcutaneous tissue. Such displacement is easily eliminated, however, if immediately after placement of the band, a hand is slipped beneath it and the folds of the skin and subcutaneous tissue are smoothed symmetrically and bilaterally, which is a simple procedure. When the band has been definitely fixed in position, the apex of the heart and the Wilson positions may be localized once more. In practice, corrections of this sort are not often necessary, as the tension around the thorax is always the same. The electrodes are quickly and easily applied, the heads of the rivets having passed through the perforations in the rubber at the positions previously marked with stamping ink. Any number of electrodes may in this way be fixed in desired positions at the same time, both on the right and left sides of the thorax as well as on the back.

The greatest advantage of this method is that it makes it possible to work with a quiet and relaxed patient. Once the patient is calm after the initial fright of the application of the band, the

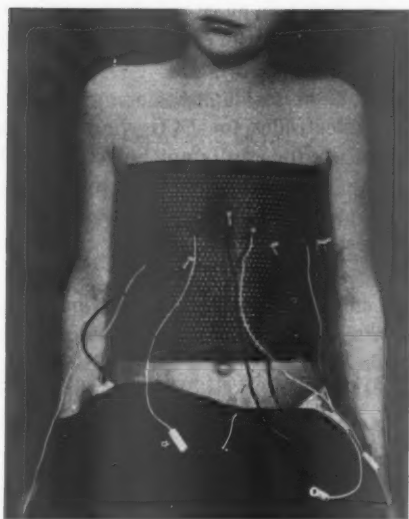


Fig. 1.

examination may be started. If the child is noisy, frightened and crying, it is best to leave it with the nurse or mother, once the electrodes are applied, and go to another room, returning only when it has become calm. When possible the registration should be made from behind a screen or from a window of an adjoining room, thus without the knowledge of the patient. Muscular disturbances and sympatheticotonus are diminished and there is no risk of displacement of the electrodes. In ECG examinations with subcutaneous ergotamine, firmly applied electrodes are advantageous. When the second ECG registration is made 45 min. after the injection, the child is often asleep and vagotonus is further increased. This type of electrode band is also of great importance when functional tests are carried out on stairs or on a bicycle, as the registration can be made immediately at the end of the exercise, and no time is lost for couplings. The band is also advantageous when precordial ECGs are registered during cycling.

The electrodes stay firmly in place and their positions can be varied with the greatest ease while the examination is in progress.

### Summary

The choice of electrodes for ECG chest leads in children is discussed, those in use for adults not being advisable. An elastic band covering the entire thorax, whereby electrodes of small diameter can be applied anywhere on the chest, is described.

### Résumé

On discute le choix des électrodes pour conducteurs de poitrine ECG pour enfants, ceux employés pour les adultes ne pouvant être recommandés. L'auteur décrit l'emploi d'une bande élastique couvrant tout le thorax, qui permet d'appliquer des électrodes de petit diamètre sur n'importe quelle place de la poitrine.

### Zusammenfassung

Die Elektroden von Ekg-Brustleitungen für Erwachsenen sind für Kinder nicht geeignet. Es wird ein elastisches Band beschrieben, das den ganzen Thorax bedeckt, sodass kleine Elektrode an beliebiger Stelle fixiert werden können.

### Resumen

Se discute la elección de los electrodos de pecho para conductores ECG para niños, siendo irrecommendables aquellos empleados para adultos. El autor describe el empleo de una banda elástica que cubre todo el torax, lo cual permite aplicar electrodos de diámetro pequeño sobre cualquier lugar del pecho.



## CASE REPORTS

### Lymphogranuloma Inguinale in Children

#### Report of 2 cases

by

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Lymphogranuloma inguinale (Lgrl. venereum) is a rare disease in pediatrics. In the literature we have so far found only 26 cases in children, — 2 boys, 24 girls — seven of which are reported by Sonck from Finland. The severe chronic form of the disease with rectal stricture was observed in 12 cases (Bensaude, 1934; Elitzak and Kornblith, 1935; Dick, 1936; Banciu and Caratzali, 1938; Sonck, 4 cases 1939; Gulowsen, 1939; Sonck, 1940; Winge, 2 cases 1941). Joint manifestations, chiefly hydrops genus, were found in 6 cases (Banciu and Caratzali; Sonck; Winge). The case reported by Banciu and Caratzali was one of venereal infection of the rectum through coitus perversus. In the other cases there are no indications of the children having been infected through sexual intercourse. In most cases they had obviously been infected by their parents. They had slept with their infected mothers in the same bed, or used the same lavatory. In one patient a common enema tip was the apparent carrier of the infection.

There seems to be no essential difference in the course of the disease in adults and in children. For a long time sulphonamides have been successfully used in the treatment, good results have also been obtained with aureomycin.

Two of Sonck's cases with rectal stricture (the girls Nita and Sirkku) have died, the rest have recovered. It might be remarked that the girls Kaija and Kyllikki, who both suffered from a severe stricture, only passable to a pencil, and who still in 1943 were reported to have some difficulty in defaecation were later completely cured with sulphonamides.

The prognosis of the stenosing proctitis due to lymphogranuloma inguinale seems to be good, in children as well as in adults, if the treatment is begun before the infection has lasted for more than 6 years.

We will now discuss two new cases of rectal stricture due to lymphogranuloma inguinale in children, seen at the Children's Hospital in Helsingfors.

We have gone through the complete records of the hospital, from 1918 up to 1949 (in all 36 089 patients treated in the hospital), without

being able to find a single case of inflammatory stricture of the rectum other than these two, and one earlier case, described by Sonck in 1940. During this period 16 other cases have been treated at the Children's Hospital with the diagnosis *strictura recti*, on closer examination they have, however, proved to be merely sequelae of congenital anal atresia.

*Case 1.* Anna-Liisa L., born 1931, worker's daughter, Maaninka. Birth normal. The patient is the sixth of seven children. She used to be healthy, but about 1942 or 1943 she developed suppurating buboes in both groins. Shortly afterwards symptoms of proctitis became manifest: Discharge of blood and pus from the rectum, with tenesmus and pains, and gradually increasing difficulties in defaecation. She had no eruptions, nor any inflammation of the joints.

At the Children's Hospital Aug. 15—Aug. 26, 1945 (no 1043) and at the II Surgical Clinic Aug. 26—Sept. 29, 1946 (no 1522) dg. *Lympho-granuloma recti*.

Condition Aug. 26, 1945: General condition rather good. Heart and lungs healthy, in both groins scars of bubonic fistulae. Wassermann and Kahn reactions negative, sedimentation rate 81 mm, tuberculine test (Mantoux 0.1 mg) positive. Hb 63/79, E 4.939.000, L 3.600.

The rectal wall is infiltrated, but smooth, the mucous membrane is oedematous, bleeds easily, partly eroded, partly covered with light grey membranes. 5 cms inside the anus there is a rigid stricture passable only to a pencil. Barium enema, see fig. 1.

Aug. 30, 1945 Frei test positive (with 2 antigens).

Sept. 14, 1945 Frei test positive. Control reactions on two other patients negative.

In the hospital the patient had, in all, 3 2-sulphanilamidothiazol-courses, 0.5 gm  $\times$  60, each, or 90 gm in all. When the patient was discharged the stricture felt somewhat softer but as narrow as before.

The patient writes on the 31st of Jan. 1950, that she is quite well and that she has no symptoms now. She has not had any treatment since leaving the hospital.

*The mother* (case no 560) born 1896, had buboes in both groins some time in the 1930s, but cannot tell the exact year. Soon after that she developed chronic proctitis, which has now been troubling her for several years. Discharge of blood and pus from the rectum. Great difficulty in defaecation. She has never seen a doctor.

Aug. 9, 1946: Infiltrated cock's-comb-like excrecences at anus. Discharge of blood and pus from the rectum. The whole rectum is transformed into a rigid tube with a very compact infiltration of the wall; the lumen hardly allows the passage of a pencil. Frei test faintly positive.

*The father* denies having had any buboes. Aug. 9, 1946: Frei test faintly positive (control reactions on two sons negative).



Fig. 1.

*Case 2.* Maila L., born 1935, worker's daughter, Muolaa. Birth normal. No buboes were observed. Even as a little girl she had difficulties at times with bowel movements, which were explained as constipation. More obvious inflammatory symptoms from the rectum, such as discharge of mucus and blood, have been noticed only since 1944 or 1945. The troubles have gradually increased. The patient has had no erythema nodosum nor any solar eruption. A swelling of the ankle was noticed once, after a long walk, but she has had no other rheumatic trouble or swellings of joints.

The patient was treated, because of rectal stricture, at the Children's Hospital Feb. 14—March 25, 1948 (No 810). Dg. *L. i. Proctitis chr. et strictura recti.*

Condition Feb. 14, 1948: The patient is somewhat pale but her state of nutrition is quite good. Heart, lungs and urine are normal. Wassermann and Kahn reactions are negative, sedimentation rate 46 mm. The joints are healthy, no eruptions, no enlarged lymph glands. There is a small cock's-comb excrescence at the anus, but no fistulae. In pars sphincterica recti an oedematous infiltration can be palpated running lengthways at the posterior wall. 5 cms inside the anus there is a very tender, rigid, canal-shaped stricture, not allowing even the passage of a fingertip. There is no cavity of the ampulla recti. The stricture is passable to Hegar 12. The rectal mucosa bleeds easily and it is injected and covered with purulent mucus. Barium enema reveals that the whole of the rectum is transformed into a narrow tube. The wall, however, seems to be unusually smooth and even. At the sigmoid flexure the colon resumes its normal width.

Barium enema March 19, 1948: The rectum still only the size of one finger. It is especially noted that the junction of the rectum and the sigmoid flexure is only about the size of a pencil. As on the previous occasion, the upper parts of the sigmoid flexure and the colon are normal. On X-ray examination, then, no enlargement of the narrowed rectum has been observed.

The patient was treated with 2-sulphanilamidothiazol 0.5 gm 6 times daily for 38 days (114 gm in all), and with 2-phtalylsulphanilamidothiazol 0.5 gm 6 times daily for 36 days (108 gm). She was given, besides, liver extract, vitamins A, C, and D. On leaving the hospital she reports having no particular difficulty with bowel movements.

Nov. 26, 1948. The sulphonamide treatment has favourable influenced the inflammation and the rectal discharge has stopped. Anus is healthy. The caudal part of the ampulla now seems to be of normal size, the walls are smooth and pliable, but in the middle part of the ampulla the finger encounters a funnel-shaped stricture that leads into a narrow canal, which can be passed by Hegar 12, only with great difficulty and pain.

The patient writes Jan. 28, 1950 that she is in a better condition than before, but she has still some difficulties in bowel movements and sometimes some discharge of pus from the anus. She has not had any treatment since leaving the hospital.

*The mother* (case No 226), born 1915, had, during this pregnancy noticed a slight tenderness in the rectum. The rectal difficulties she had later on were quite insignificant throughout, according to her. Not until one or two years afterwards did she notice for the first time that she suffered from eruptions when exposed to sunshine. At the time she had a genital ulcer, which she showed the doctor when she showed him the eruption. (The daughter was then about 1 or 2 years old.)

March 3, 1948: In good condition, Wassermann and Kahn reactions negative. Frei test positive (antigen 'LEH'). Sedimentation rate 30 mm.

In the lower part of rectum the wall is somewhat uneven, but only a few and rather insignificant nodular excrescences can be palpated. She has probably had a proctitis that is now about to heal. (She has taken sulphonamides several times.) The mother says that, if her memory is not at fault the father had a bubo inguinalis before the birth of the daughter. He was treated in Viborg District Hospital, but unfortunately no dates are obtainable, the case histories having been lost during the war.

The above cases show on the whole the same characteristics as a great deal of the earlier reported cases of lymphogranuloma inguinale in children with there rectal strictures, and with the most probable source of infection in their mothers.

### Summary

Report of two new cases of lymphogranuloma inguinale (lgrl. venereum) in young girls — 13 and 14 years old — with severe rectal strictures. These are the 8th and 9th cases of lymphogranuloma inguinale in children seen in Finland. Both children were probably infected by their mothers, who were suffering from the same disease with rectal manifestations.

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## Two Cases of Thallium Poisoning

by

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Owing to its property of causing a loss of hair thallium earlier was commonly used as a depilatory in treatment of fungus of the scalp in children. It was usually administered perorally in the form of acetate, in one dose of 6–8 mg/kg body weight. However, as the treatment even with a correct dosage frequently caused poisoning, in several cases with a lethal outcome (1) the administration of thallium for this purpose has now been superseded by X-ray depilation. Thallium salts have, on the other hand, come increasingly into use as a rodent poison, for which purpose they are eminently suitable, being odorless and tasteless and not immediately lethal. The cases of thallium poisoning reported in recent years have commonly been caused by rat poison (usually kernels of wheat prepared with thallium sulfate or a thallium paste) which have been ingested by mistake or with suicidal intention. Only few such cases have hitherto been reported in Scandinavia (2–6), wherefore the following case reports have been deemed of interest.

*Case 1.* K. L. B. 1404/49. Boy, aged 6. Previously healthy with the exception of uncomplicated scarlatina in Oct. 1949. Around Dec. 10, 1949, he began to have pains in his legs and had difficulty in walking; he was periodically unable to sleep because of the pain. December 24 his hair began to fall out. Admission to the medical department of K. L. B. Dec. 28. His general condition was good. Physical examinations revealed a slight muscular weakness in the legs, especially the left leg, and a marked diffuse loss of hair over the entire head. All reflexes normal. No decrease of sensibility. The blood showed nothing remarkable with the exception of a slight relative lymphocytosis. S. R. normal. Urine: O. EEG and spinal fluid showed no pathological changes. Thallium poisoning was suspected but at first no history of this could be elicited. An examination of the urine Dec. 31 according to Crabbe's electrolytic method also failed to reveal thallium. However, the suspicion remained and was later confirmed (see below). During the period following the loss of hair progressed to nearly total alopecia, while the "polyneuritis" pains disappeared with rest in bed and the muscular strength of the lower extremities improved by degrees. Treatment with Vitamin B in large doses was instituted Jan. 5 and was continued for three weeks without

any appreciable effect. Discharged Jan. 26. At follow-up examination Feb. 23 the patient was in good general condition, had gained weight and walked nearly normally. New hair had not as yet begun to reappear.

*Case 2.* K. L. B. 1405/49. Boy, aged 7. Playmate of the patient described above. Had also had uncomplicated scarlatina in October, and had previously been healthy. Had an onset of the same symptoms, at the same time, as his playmate, and was admitted to this hospital simultaneously with him, Dec. 28. The loss of hair was not as pronounced as in the former patient but the "polyneuritis" symptoms were more pronounced, with a definite wasting of muscles mainly in the right leg. The blood showed a slight eosinophilia and a relative lymphocytosis. Urine, S. R., EEG, and cerebrospinal fluid normal. Vitamin B therapy instituted Jan. 5, and after the definite establishment of the diagnosis dried yeast (see below) was also administered in daily doses of 10 g. The pain gradually disappeared with rest in bed and the strength of the legs improved slowly. Discharged Jan. 26. At follow-up examination Feb. 23 the general condition was considerably improved with a good gain in weight, improvement of the muscle wasting and some reappearance of new hair.

The definite diagnosis of these cases was not made until about five weeks after the assumed poisoning. On closer investigation it was found that the boys had managed to find their way into the loft of a shop that usually was locked; there they had found and eaten a wafer prepared with thallium sulfate and put out as ratbait several weeks previously. A chemical analysis of the urine sent for examination Jan. 3, 1950, thus about one month after the poisoning had taken place, showed the presence of considerable amounts of thallium. That the previous urinalysis had given negative results must be ascribed to a lower degree of sensitivity in the method then used.

The symptomatology in thallium poisoning has previously been described both in surveys (7) and in case reports and is, therefore, not discussed further in the present paper. The presence of "polyneuritis" of the lower extremities in association with loss of hair is very suggestive of the diagnosis, even though these symptoms are not pathognomonic. In order to establish the diagnosis there should be a definite history of ingestion of thallium or/and the demonstration of the metal in the urine. The latter is often feasible even if several weeks have elapsed since the poisoning occurred.

As therapeutic measures the intravenous or peroral administration of sodiumthiosulfate or sodiumiodide has been recommended, possibly also BAL, and Vitamin B for the "polyneuritis." Judging from the literature, however, opinion diverge concerning the benefit of these measures.



Fig. 1. About 10 weeks after thallium ingestion. Diffuse loss of hair still present.

Recent animal experimental investigations (8, 9) have, on the other hand, shown that both cystine and especially dried yeast and, to a lesser extent, methionine have a definite detoxicating effect in chronic thallium poisoning, while the effect of Vitamin B in this respect is comparatively slight. BAL does not seem to have any effect whatsoever (9). According to the experiments cited it thus seems as though thallium has an inhibitory effect on the cystine metabolism of the organism, though the exact mechanism of this as yet is obscure. — In acute poisoning thallium is excreted with the urine over a prolonged period of time, as mentioned above. Even if the diagnosis is not made until after several weeks (as is often the case) one may expect some benefit from treatment with cystine or dry yeast in these cases as well. In the present cases, the patient showing the most pronounced "polyneuritis" symptoms received dried yeast over a period of about six weeks, the other patient not being given yeast. No manifest difference in the course was established, however.

Even though thallium poisoning in children caused by the ingestion of rodent poison has been comparatively infrequent so far, it is obvious that the use of thallium as rat poison involves very great risks. It should at all events not be used in the form here described; that is to say in the form of food attractive to children. The statement that thallium containing rat poison is only to be put out in localities inaccessible to children is of limited value, as appears from the present cases.



### Summary

Two cases of thallium poisoning in children after the ingestion of rat poison are described. In such cases, treatment with cystine or dried yeast is worthy of trial.

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## Primary Cancer of the Liver in a Boy Aged Two Years

by

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*Chief: O. ELGENMARK, M. D.*

A boy of 2 years (Case 128/50, H. M., born Jan. 10, 1948) with juvenile cancer of the liver has recently been attended in the Children's Department of the Nyköping Hospital. As the case offers certain points of differential diagnostic interest, a brief account of it is submitted below.

The patient was brought to the Children's Outpatient Department on account of a cough on Feb. 9, this year, whereupon a considerable enlargement of the liver was found. He was therefore admitted for further investigation. He had been attended in the department twice before, Nov. 1948 and Sept. 1949, on both occasions for convulsions connected with infections of the upper respiratory passages, dyspepsia and hypoglycaemia with a fasting blood-sugar level of 0.030 and 0.040 % on the respective occasions for which no cause except the dyspepsia could be demonstrated. On both occasions Heller's and Almén's tests were negative; Legal's showed a trace. Glucose and adrenalin tolerance curves were unfortunately not made, as the trouble vanished each time on cessation of the infection. Nothing abnormal was palpable in the abdomen; the liver was not enlarged on either occasion. At later visits to the Children's Outpatient Department, the last on Dec. 6, 1949, liver palpation also gave normal findings.

On admission Feb. 9, 1950, the patient had a mild infection of the upper respiratory passages and was somewhat sluggish but fairly unaffected in other respects. His length and weight were respectively, 85 cm and 11.7 kg, *i.e.* slightly below the average for his age. Palpation showed the liver to extend down to the umbilical plane, with a firm, rounded margin and smooth surface. Laboratory Values: blood sugar 0.095 %; hb. 57 %; w.b.c. 6 400; diff.: nothing remarkable; Meulengracht, 1: 7; thymol, 1.0 unit; Takata, neg.; cholesterin, 375 mg. per 100 cc.; Heller +; Esbach, 3 per mille; Almén + (later neg.); Benedict, 0.6 %. Sediment: solitary red, 20—40 white, moderate epithelia, no casts. Glucose tolerance test (11 g) showed a maximal blood-sugar rise to 0.148 per 100 cc. after 15 min. declining to below initial value after 45 min. Adrenalin tolerance test (0.4 ml) showed a maximal blood-sugar rise to 0.200 per 100 cc after 60 min. with return to 0.106 after 150 min. X-rays of skull: negative. Skeletal development retarded, 20 centres of ossification as against an average of 36 for his age and 25 for his length. The especially early tendency he showed to hypoglycaemia with acetonuria, hepatic enlargement, delayed development and hypercholesterolaemia suggested glycogen disease, which could also account for the albuminuria. However, the glucose and adrenalin tolerance curves were atypical, with a low and rapidly regressing glucose tolerance curve unlike that in glycogenosis and good sugar excretion on adrenalin. On examination of the abdomen a few days later the presence of a tumour was suspected, as the following report shows.

*X-rays Feb. 12:* "The liver is considerably enlarged. Corresponding to its right posterior part there are scattered, reticularly arranged calcifications. In the posterior margin of the stomach there is a rounded concavity. The lower pole of the right kidney appears to be of normal size; otherwise the kidneys cannot be demarcated. It cannot be decided whether the calcification lies in an enlarged liver or in a tumour seated behind the liver and originating from the kidney or suprarenal capsule" (S. Jonsell).

On the day following the x-ray examination the patient had an extremely violent gastro-enteritis and died the next day in spite of intensive therapy.

Autopsy disclosed a rounded, macroscopically well-defined tumour larger than an adult's fist that permeated practically the whole right lobe of the liver, bulging considerably forward on the posterior lower surface. In the tumour there were profuse bleedings and calcareous hollows the size of rice grains. The right lung was the seat of disseminated atelectasis. Nothing abnormal was found in other organs; no metastases observed. Histodiagnosis: "Microscopic examination shows that the tumour consists of large alveolar formations of epithelial cells, which seem to be of

two kinds. They are separated by rather thick septa of vascularized connective tissue from which slender capillary vessels extend in profusion into the solid epithelial cones. Some of the epithelial cells are small and poor in protoplasm, with rather large nuclei very rich in chromatin; others are large and rich in protoplasm with looser nuclear chromatin.



Fig. 1.

In appearance the latter are highly reminiscent of liver cells. There is no distinct boundary between the different cell layers, which pass directly over into one another. Hence it is a question of a cancer that in all probability has sprung from the liver parenchyma. The other organs examined exhibit no remarkable changes. Histodiagnosis: Cancer hepatitis juvenilis" (A. Bergstrand).

In a paper printed in the *American Journal of Diseases of Children* M. STEINER made a collection of the cases published up to then of primary hepatic cancer in children up to 16 years of age. Of 105 cases analysed, he considered the diagnosis to be reliable in 75. The others were not approved on account of no histodiagnosis or an uncertain one. Besides these cases, he had 2 himself, making 77 in all.

The age distribution of these was as follows:

Age	No. of Cases	Age	No. of Cases
Birth to 2 Mos. ....	2	7 to 8 Yrs. ....	1
2 to 6 Mos. ....	8	8 " 9 " ....	1
6 Mos. to 1 Yr. ....	18	9 " 10 " ....	4
1 to 2 Yrs. ....	13	10 " 11 " ....	1
2 " 3 " ....	0	11 " 12 " ....	4
3 " 4 " ....	3	12 " 13 " ....	3
4 " 5 " ....	1	13 " 14 " ....	5
5 " 6 " ....	4	14 " 15 " ....	4
6 " 7 " ....	3	15 " 16 " ....	2

Thus in 41 cases, or 53 %, the tumour arose before the age of 2 years and was already present at birth in one of the cases.

The sex incidence was 51 boys (68 %) and 24 girls (32 %); in 2 cases the sex was not stated.

As regards the aetiology, STEINER, with special regard to the age distribution and to the case in which the tumour had already arisen before birth, considered an embryonic primordium to be decisive in juvenile cancer of the liver. In only 2 of the cases had hepatic cirrhosis occurred at the same time, both of them in older children.

The symptomatology was not characteristic and depended mainly upon pressure of the tumour. Pain in the hepatic region was common and anorexia with emaciation frequent, though in many cases the nutritional state was good. Icterus and ascites were uncommon, icterus occurring in only 6.5 % and then owing to mechanical pressure on the bile ducts.

The course was usually insidious, with the circumference of the abdomen gradually increasing. Calculated from the onset of symptoms, the average length of life was four months and all cases had a fatal issue. Operation was performed in 4 cases.

With reference to the morbid anatomy, with the gross appearance of the tumours as a basis they were first classified as massive, nodular or diffuse, but the authors later adopted a histologic division into hepatomata emanating from the liver cells and cholangiomata springing from bile duct cells. Of the cases accounted for, 52 were hepatomata and 3 cholangiomata, while 22 were not classified.

Metastases had occurred in 22 cases (27 %), in 16 of them to the lungs and in 9 to the lymph glands. In the pleura, pericardium, spleen, and pancreas metastases had occurred in one case each.

Concerning the differential diagnosis STEINER points out that other diseases associated with enlargement of the liver in children must ob-

viously be taken into account, *e.g.* other tumours, congenital cysts, echinococcus cysts, hepatic abscesses, leucaemic liver infiltrates as well as toxic and inflammatory hepatic enlargements, *e.g.* syphilis.

From the cases published here it is evident that to a very high degree the symptoms may resemble "Speicherungskrankheit" of the glycogenotic type. The extent to which the earlier tendency to hypoglycaemia demonstrated in the Nyköping case was associated with the patient's tumour or was a spontaneous process independent of the tumour can naturally not be decided. The long time that elapsed between the first observed hypoglycaemic attack and the direct symptoms of tumour compared with the rapid development in the final stage would seem to make it less probable that the tumour as such was the cause of the hypoglycaemic attacks. A more probable assumption would be that the liver disturbance which had brought about the attacks may have contributed to the development of the tumour and possibly constituted a precursor to it.

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### A Case of Infantile Amaurotic Family Idiocy

by

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In 1881 the English eye specialist WARREN TAY (1) described the characteristic fundus changes of the eye caused by this disease, which has been named after him and the American physician, BERNARD SACHS. In 1887 the latter (2) established the clinical and pathologic characteristics of the disease, which in 1896 he called infantile amaurotic family idiocy (3). As the name indicates, it is familial, and occurs as a rule among Jews, very often when the parents are cousins. Jewish families originating from the Polish provinces formerly belonging to the Russian empire are those most often affected. In exceptional cases non-Jews are also affected, however. HARBITZ (4) in Oslo found in 1913 that of the 86 cases published, 61 were Jews. After a critical review of the literature Roos (5)

SCHEERSTADT INSTITUT FÜR MEDIZIN

of Chicago found in 1935 only 2 definitely non-Jewish cases, and he included only those verified by pathologic-anatomic diagnosis. Roos described one case of Norwegian origin in which the parents were not related.

The cause of the disease has not yet been discovered. It usually comes under the reticuloendotheliosis group with changes mainly in the nervous system. The attention of PICK (6), HAMBURGER (7), LINDAU (8), SCHLESINGER, GREENFIELD and STEIN (9), and W. OF DEN WINKEL (10), has been drawn to it owing to its relationship with the Niemann-Pick, the Gaucher, the Hand-Schüller-Christian, and the Letterer-Siwe diseases. Most people, *e.g.* MOTT (11), think that the disease is hereditary; according to FALKENHEIM, STEWART, and ABT this can be proved by means of genealogical trees which show a number of cases in the same family. According to HERRMAN (12), sometimes only one of twins may be affected. SACHS and HAUSMANN (13) say that girls are affected about three times as often as boys.

Amaurotic idiocy of the Tay-Sachs type is very rare in Sweden. Hitherto only 10 cases have been reported, 5 by WALLGREN (14, 15), 2 by NORDLÖW (16), and 3 by LINDAU (8). Apart from these, several cases of amaurotic idiocy have been described in Sweden which were not of the Tay-Sachs type. In 1939 BRANDBERG (17) reported one case of late infantile type with pathologic changes similar to the type of infantile diffuse sclerotic meningitis described by KRABBE. BRANDBERG's patient had also had two brothers whose disease presented the same pathologic picture. Furthermore, SJÖGREN (18) and ROSENGREN (19), among others, have described several cases of juvenile amaurotic idiocy of the Vogt and Spielmayr type. This disease is to be met with in children between the ages of 6—14, shows no macular changes and is not confined to any particular race.

In 1947—48 a boy suffering from amaurotic idiocy of the Tay-Sachs type was treated at the Samariten Children's Hospital in Stockholm. The parents were Jews and cousins about 30 years of age and traced their descent from Eastern Poland. The patient had several cousins, all of whom were in good health. From the medical point of view there was nothing special in this family except that one sister had shown the same symptoms as the brother.

The mother was in good health throughout pregnancy. The birth was normal. The child weighed 4250 gm and was breast-fed and under medical control. At the age of 3 months he was seized by some transitory attacks during which he became blue and rigid. When he was 5 months old his development began to be arrested and later on it declined. The body became limp and the child was hypersensitive to sounds; he started at the slightest noise and this state gradually increased. He was able to babble at the age of 5 months, but at the age of 1 year he was no longer

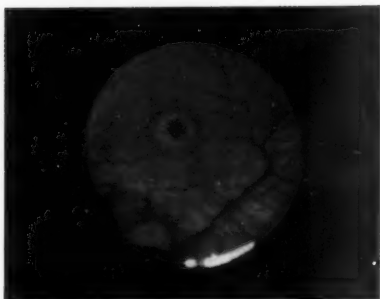
capable of doing so. At 6 months his laugh became unnatural and there was a rattling noise in the throat. When he was 7 months old he started taking hold of objects but later on he lost this power completely. When 8 months old he began to shut his eyes and wink; his eyelids began to tremble when he was lying on his back, then his body became rigid with arms and legs stretched out. His sight then began to decline, his expression became bewildered and he was unable to fix his eyes upon anything properly. When 8  $\frac{1}{2}$  months old he had difficulties in sitting even when supported and some time later he could no longer sit at all. At the age of 1 year the boy could no longer hold up his head and it dropped flaccidly when he was held up. The first teeth came when he was 15 months old.

When he was brought to Samariten at the age of 15 months he was mentally deranged and in addition was suffering from bronchopneumonia. This was treated in the usual way and he soon recovered. His head and chest were 48 cm and 46.5 cm in circumference, respectively, and the length of his body 79 cm. The heart was normal as well as the cardiogram. The liver was soft and could be palpated one finger's breadth below the arcus; the spleen was normal near the arcus. The usual examinations of the blood and the urine did not show anything remarkable. Wa.R. neg.

The patient was an idiot. His body was hypotonic but periodically rigid. During the last months of his stay at the hospital his extremities became spasmodic. He was unable to babble. His expression was bewildered without nystagmus; his eyelids often quivered. He was nearly blind. The pupils were a little irregular and sometimes varied in size and reacted only a little to light, also consensually. The most characteristic sign was perhaps hyperakusis. At the slightest noise the child started and threw up his arms and the trembling began in his eyelids. Sometimes he was far less sensitive to sounds. When put on his back he started whining. Occasionally erythema appeared in his face. During his last months he had attacks of spasms when his position was changed. He was constipated throughout his stay at the hospital.

Corneal and pharyngeal reflexes were reduced. He had difficulties in coughing, clearing his throat and swallowing. The reflexes of the extremities were normal, though Trömner and Babinski were positive on both sides. When the Oppenheim reflex was tested on one side, both big toes rose simultaneously. The abdominal reflexes were normal and the cremasteric slightly positive. Magnus' and de Kleijns' phenomena (20) were negative at first; later on they became slightly positive. (When the child's head was turned to one side the arm and the leg were stretched out on the same side, but at the same time the extremities on the other side were bent.) Electrical examination was normal.

The x-ray examination of the skull was normal. The development of the ossific centres ad modum ELGENMARK (21) was normal. Four different



lumbar punctures showed neither an increase in the cells nor albumen in the fluid, in which cholesterolin could be found in small quantities, while in normal fluid according to Flexner it would be lacking. The values were 0.35, 0.58, 0 and 1.1 mgm%. In control tests from normal cerebrospinal fluid cholesterolin could not be discovered. Contemporary tests of the total cholesterolin in the blood plasma showed a pathologically high value in 1 test and in 2 the highest normal limit, 213, 171, 190 and 145 mgm%. The examination of the fundi of the eyes showed poor pigment and pale atrophic papillae and on both sides in the region of the macula

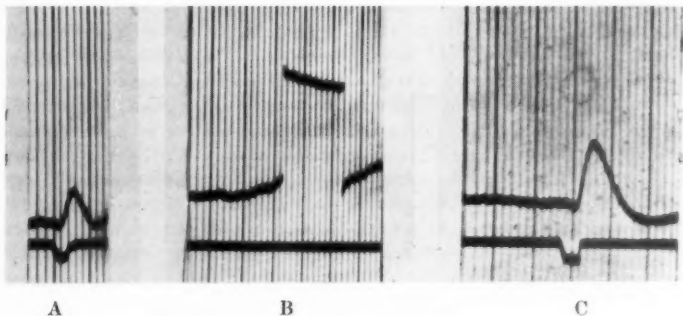


Fig. 1. Electroretinogram curves.

The action potential from the retina on brief illumination is recorded.

A = electroretinogram of patient's left eye. The upper curve = the eye potential; the upward wave, the b potential is 0.16 mV. The lower curve is a record of the stimulus light, 80 Lux; the eye is dark adapted. Time: 0.1 sec. between the thick lines marking time.

B = calibration for 0.5 mV.

C = normal electroretinogram from normal eye, the b potential is 0.33 mV. Curve A shows that the electroretinogram is slightly pathologic of the sub-normal type.



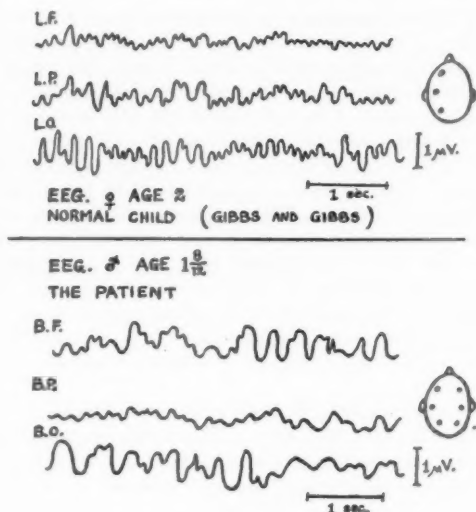


Fig. 2.

lutea cherry-coloured round spots surrounded by a grey-white zone (Dr. Y. LINDBLAD). A colour-photo of the fundi of the patient was taken at the eye clinic of Karolinska sjukhuset with a Nordenson-Zeiss camera which was adapted for colour photo (see photo). An electroretinogram (ERG) (22), probably the first made in this disease, simultaneously was taken by Prof. KARPE. The action potential of the retina was found to be slightly pathologic of the subnormal type. The ERG examination indicated that the peripheral function of the retina was injured less than the central one (KARPE). (See Fig. 1 with explanations.) An electroencephalogram (EEG) was taken by Dr. B. HOLMGREN at the mental clinic of Karolinska sjukhuset. It showed an intense general dysrhythmia of low frequency. No definite points could be found for well limited focus, although discrepancies could be discovered between the left and right hemispheres. In view of the age the finding can be considered pathologic (FREY, HOLMGREN). (See Fig. 2.)

During his 8-month stay in the hospital the patient declined both mentally and physically. He lost 3.5 kg in weight so that finally his weight was only 7.2 kg. During the first five months the circumference of his head diminished 1.5 cm but during the last three months it increased 2 cm. The patient died at the age of exactly 2 of increasing marasmus.

Post-mortem examination was carried out by Dr F. WAHLGREN and showed nothing remarkable in the internal organs; liver and spleen were normal. NASSAU's finding of fat-marrow in the long bones of the extremities poor in cells was not present in this case. The marrow had a normal dark-red colour. A sternal puncture in vivo had shown a reactive bone-marrow without specific features but the reticulum was extremely hyperplastic. The weight of the brain was 1500 gm without any manifest hydrocephalus. A microscopic examination of the brain carried out by Dr. A. BERGSTRAND confirmed the diagnosis. In the cortex cerebri the ganglion and probably the glia cells as well were extremely deformed and transformed into big balloon-shaped cells with a peripherally situated nucleus containing vacuoles. A lipidlike substance could be shown in the cytoplasm by means of various fat-staining methods. The white substance was considerably atrophied and the myelin was dissolved from the nerve fibres, in which it was not possible to discover any axis cylinders.

The patient had a sister who apparently suffered from the same disease as the brother. Her development was normal up to the age of 5 months, then the same symptoms appeared as in her brother: an increased sensitivity to noise, flaccidity, mental decline, blindness, etc. She died quickly of pneumonia at home nearly 15 months old.

It is probable that the Tay-Sachs disease is more common than may be supposed and that not all cases are diagnosed but are only classified as idiocy etc.

*Summary.* After having reviewed literature on infantile amaurotic family idiocy (Tay-Sachs type) a report is given of such a case. The blood cholesterin was found to be higher in at least 1 test and cholesterin was also traced in the cerebrospinal fluid. For the first time a colour-photo of the fundi of the eyes, an electroretinogram and an electroencephalogram have been published in a case of this disease.

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## PROCEEDINGS OF PEDIATRIC SOCIETIES

### Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society.

Meeting, May 25, 1949.

#### *Stig Sjölin: A Case of Haemolytic Anaemia.*

A case of macrocytic haemolytic anaemia in a 12-year old girl is described. The disease had probably begun with acute hepatitis, but no signs of it were noticed during the hospital stay. The number of red corpuscles varied from 1.3 to 2.3 millions, the reticulocytes from 9.3 to 21.4 per cent, the mean corpuscular volume from 96 to 104  $\mu^3$ , and the bilirubin percentage of the blood from 0.7 to 1.5 mg per 100 cc. The fragility of the red corpuscles in hypotonic saline solutions was moderately increased. A few spherocytes were perceptible. There proved to be autoagglutinins in the blood. The cephalin flocculation test, the thymol flocculation test, and the Takata-Ara reaction, were positive. The total blood protein had sunk to 5.7 %. An electrophoretic analysis of the serum showed an increase of the gamma globulins to 2.4 %.

The case was taken to be one of acquired haemolytic anaemia (no known blood diseases in the family, macrocytosis, autoagglutinins). Considering the recent hepatitis and the disturbances in the blood proteins, it is not unlikely that there was a liver lesion also. Such a lesion might have been the actual cause of the haemolytic anaemia.

All therapeutic measures, including a high protein diet and three blood transfusions, failed. After an illness of four months the girl died, her symptoms being those of acute peritonitis. An autopsy was refused by the parents.

#### *Olof Mellander: On the Pathogenesis of Rickets.*

Some balance experiments with enzyme-resistant phosphopeptides from casein were performed on infants. The calcium salts of these peptides contain about 6 % phosphorus and 10 % calcium and are so easily soluble that at least 50 % solutions can be prepared. The balance experiments with these peptides (from cow's casein) demonstrates that a considerable part of the calcium given in this form is absorbed from the intestinal tract. The peptides have no allergic properties and can be injected intravenously into animals (rabbits and guinea pigs). It may be that they are the physiological substrate to the phosphatases in the ossification process as interpreted by Robison.

*R. Berfvenstam and O. Mellander: The Digestion of Proteins in the Stomach of Premature Children.*

A small number of premature infants have been investigated for their ability to digest and absorb proteins in the stomach. Casein from human and from cow's milk was introduced into the stomach by tube, and taken up again after an interval of 10—15 minutes. Similar experiments were performed with human gamma-globulin. The recovered samples were subjected to electrophoretic analyses, and their nitrogen-phosphorus ratio determined. During the experiments the amino-nitrogen in the blood of the infants was also followed. The electrophoretic patterns show that digestion is possible at the fairly high pH prevailing in the stomach, but the experiments performed so far do not give any evidence of absorption from the stomach.

Meeting, Oct. 14, 1949.

*A. Wallgren: Some Aspects of Medical Training in America particularly as Regards Pediatrics* (published in Svenska Läkartidn. 1949).

*M. d'Avignon and B. Vahlqvist: A Case of Cystine Disease.*

The authors describe a case of cystine disease in a 14 month old boy. The albumin metabolism and nitrogen excretion in the urine were subjected to thorough study. Case published in Archives Françaises de Pédiatrie 1949.

*Bengt Jonsson: A Case of Haemosiderosis Pulmonum.*

Report on a case of lung haemosiderosis in a boy 5  $\frac{1}{2}$  years old. The disease started as a grave anaemia with low serum iron but increased number of reticulocytes. It was only after the lapse of a year that typical acute attacks set in, with dyspnoea, cough, haemoptysis and changes found in the lungs on roentgen examination in the form of dispersed, cloudy infiltrates in small spots. The patient succumbed in conjunction with an acute attack after little more than one year's illness. Autopsy showed typical changes with pronounced haemosiderin deposits in the lungs, pronounced fibrosis and destruction of the elastic tissue. The pathogenesis is discussed. The case is to be published later in more detail.

*Lars Ström: Experiments with Radioactive Calmette (BCG) Vaccine.*

In Acta tuberculosea scand. Suppl. 21 1949, the author, in association with Lars Rudbäck, reported on an investigation of the distribution and the speed of dissemination of tubercle bacilli in the guinea pig organism by means of radioactive isotopes. In these we made use of a BCG culture. This investigation shows that the BCG spread and distribute themselves

in the same way as the virulent tubercle bacilli. The investigation also shows that the dissemination in the organism following intraperitoneal or intramuscular injection is extremely rapid. With a view to studying more closely the first stage of the path of the bacteria following intracutaneous injection, some experiments were made on human beings with a "marked" vaccine. The marking was achieved by adding  $P^{32}$  to the substrate on which the BCG culture was grown, after which the bacteria were deprived of their radioactive medium by careful washing. The culture on the radioactive substrate was made at the Bacteriological Laboratory, head A. Wassén, M. D., of the Sahlgren Hospital, Gothenburg. Following intracutaneous injection of these bacteria the activity was measured direct on the skin surface by means of a mobile Geiger-Müller chamber, constructed at the Wenner-Gren Institute, which enabled the path taken by the activity (i.e., the path taken by the bacteria) to be followed. The paths were clearly those of the lymph routes and the spread was fairly rapid. Thus a stretch of 18 cm was covered in 3 min. by some of the bacteria and after 10 min. probably about half of the bacteria had passed, i.e., in this case reached the nearest regional lymph gland. It was not possible in the few experiments made so far to observe any definite difference after intracutaneous injection and scarification. A considerably larger number of tests must be made, however, to be able to decide in this case whether there does in fact exist any differences.

Probably determinations must be made of the spec. activity in blood and urine — in the event of radioactivity arising in the urine this would mean among other things that the bacteria had begun to decompose and be eliminated from the body.

**P. Karlberg and J. Lind: Experiments with an Electric Capacity Method for Determining Body Surface.**

Following discussion of the difficulty of working out a height-weight formula capable of giving a body surface area valid for all ages, results obtained with an electrical capacity method for determining the surface area are described. On comparing these with results obtained with the Du Bois formula, it appears that the graph of the latter diverges from the former even during infancy. The values obtained with Edith Boyd's formula have the same tendency, but not to such a marked degree. Her formula also gives misleading values for children of abnormal body constitution.

Thus neither of these formulas can give a value for the body surface area which can be used as a correlation factor during infancy.

The electrical capacity method enables the investigator to make direct, simple, individual determinations, sufficiently accurate, that are valid for the whole period of infancy.

Meeting, Nov. 27, 1949.

*R. Kostman: Hereditary Congenital Reticulosis.*

The author describes a form of reticulosis hitherto unknown which appears to have the following features: hereditary occurrence, first appearance in infancy, occurrence of boil-like infiltrate in the skin (not a necessary condition), agranulocytosis, changes of the bone marrow, with reticulated cells and monocytoidal elements dominating in the last stages. The pathological pictures of various organs suggest reticulosis.

*E. Mannheimer: Experiences on Patent Ductus Arteriosus.*

Report on 4 atypical Botalli cases without continuous murmurs, interesting because all apparently involve individuals with cardiac insufficiency. Diagnosis was made by heart catheterization, sometimes supplemented by angiocardiography (Lind-Wegelius method or thoracal aortography). These cases are characterized by such high pressure in the pulmonary circulation (mean value 75/42 mm Hg) that the difference in pressure between the aorta and the pulmonary artery becomes less than in typical cases, with the result, that the typical continuous murmur does not arise. In addition the high pulmonary pressure is accompanied by risk of pulmonary and cardiac insufficiency.

The results obtained suggest that cases with systolic murmurs which direct suspicion to congenital heart defects and in which special diagnosis following customary clinical examination cannot be made ought to be submitted to special examinations, including heart catheterization and possibly angiocardiography. All Botalli cases should be operated on at as early a stage as possible (down to 3 years of age) and before serious or deleterious injury has arisen.

*Fritz Karlström: The Influence of Child Welfare Centres on Disease and Mortality Among Infants.*

In the five-year period 1944—1948, 23,450 children were born in Värmland County and of these 21,789 were registered at Child Welfare Centres. On the basis of treatment records from the Children's Department of the Karlstad Infirmary, the frequency of disease among children under surveillance by Child Welfare Centres and those not under such surveillance has been calculated. It was found that rickets and spasmodophilia were about ten times as frequent, acute diseases of the respiratory tract and the lungs about five times as frequent, acute diarrhoea conditions about four times as frequent and anaemia about three times as frequent among those not under Child Welfare Centre surveillance. Mortality was seven times greater. Though this ratio cannot be attributed entirely to the work of the Child Welfare Centres, yet the results of the investigation strongly support the suggestion that we devote ourselves still further to intensifying the preventive care of children.

**Karl-Axel Melin: On the Examination and Treatment of Children with Seizure Diseases.**

An account is given of the experience at the Seizure Clinic and the Electroencephalographic Laboratory of Kronprinsessan Lovisa's Children's Hospital. Pneumoencephalography is performed in cases of seizure disease only when the history suggests traumatic aetiology, when the attack has a Jackson character, when the neurologic status displays some lateral difference or when EEG shows focus or hemisphere asymmetry. EEG is employed for diagnosis and control of treatment, the latter being particularly important with tridion treatment of epilepsy of the petit mal type. The various activation methods employed include hyperventilation, sleep activation and photic stimulation. An account is given of a case in which the diagnosis could only be made after photic stimulation.

The fact that modern anti-epileptic drugs are often used in inadequate doses or on incorrect indications is illustrated by some examples. It is important that the prescribing doctor carefully acquaints himself with the ranges of employment of the various preparations and the correct dosage. Trials with discontinuation or a decrease in treatment may be made after two years of freedom from attacks, but when possible these should be made under EEG control.

Account is given of cases of seizure disease which became essentially worse in conjunction with pertussis. Pertussis immunisation is therefore advised for these patients, despite some isolated cases reported from the U. S. A. of neurologic complications following pertussis immunisation. Nevertheless a certain amount of caution is recommended, e.g., the employment of weaker vaccine and longer injection series with smaller individual doses. On observing signs of strong general reaction the inoculation series should be interrupted.

The social attitude to patients with seizure diseases should be changed. These patients should be allowed to live more normal lives to a greater extent than they do now in many cases. As far as possible they should be treated as ordinary children in play schools, ordinary schools and occupational schools and even take part in school gymnastics with the exception of apparatus gymnastics high above the floor.

**H.-O. Mossberg: d-Phenopromin in the Treatment of Obesity in Children.**

In recent years appetite-diminishing preparations for the treatment of obesity such as d, l-amfetamin (= phenopromin, phenedrin) have been described. The d-amfetamin is less toxic and more effective than the racemic form (= d, l-amfetamin). One hundred and sixty seven previously untreated corpulent children aged 7—15 were treated as out-patients, half with d-amfetamin (Afatin Astra 2.5 mg  $\times$  3) and half with



blind tablets, with restriction of diet for all. Checks were made every third to fourth week. Seventy four per cent of the children had an excess weight of 30 % or more at the beginning of the treatment. It was found that on the average the d-amfetamin group showed a greater decline in weight during the first 10—12 weeks than the blind tablet group, and the continued decrease in weight was great. On statistical treatment of the results obtained it was established that d-amfetamin had greater effect over a period of up to 20 weeks. After that the degree of statistic probability altered as the number of cases followed up for a longer time progressively decreased. Nevertheless, treatment results in the d-amfetamin group were throughout superior to the corresponding results with the blind-tablet group. Subjectively unchanged hunger and appetite in 5 % of the children receiving d-amfetamin was stated, as against 41 % given blind tablets. Secondary effects that could be ascribed to the d-amfetamin were not observed, nor was there any tendency to narcomania. d-amfetamin is recommended as an appetitediminishing preparation in corpulence.

*P. Karlberg and J. Lind: Demonstration of Carbon Monoxide in Breath Under Normal and Pathological Conditions.*

In a large number of children it was found that the CO content in the breath, and therefore in the blood, was higher than in the surrounding air. In children in hospital without signs of infections or diseases of the circulatory system and respiratory passages, the average value of the concentration in the blood, expressed in ten thousandths volume % CO, is about 15—20. For healthy school children and children in day-nurseries, the corresponding figure is 25—30. A typical 24-hour curve shows lower values during the night, while higher values are obtained after rising and still higher after physical exercise. The relatively high values in school children and day-nursery children may be explained in this way.

Among a number of sick children examined some had a higher value in repose, but they had either had a blood transfusion or were suffering from haemolytic anaemia. In newborn babies, also, the values tended to rise during the period of physiological haemolysis but fall again at the end of the first or during the second week of life. The estimations were carried out with a CO meter according to SJÖSTRAND's method. The gas reacted in the same way as CO in three different methods of estimation (including the iodine-pentoxide method). Moreover, this gas showed the same affinity for Hb as CO. It would seem, therefore, that CO is formed by the breaking down of Hb. It is known that a C atom is freed from the haemin when it is transformed into bile colouring matter or similar substances. The fate of this C atom is at present unknown. It may be that it takes part in the formation of the carbon monoxide.

*J. Lind and C. Wegelius: Angiocardiographic Studies on the Human Foetal Circulation.*

Report of direct radiographic angiocardiography with 10 exposures per second on human foetuses in legal abortions. The technical method employed combines the advantages of high film quality with a possibility of assessing the dynamic course in the heart and the circulation in both the arterial and the venous circulatory system. The foetal communications in the circulation of the human foetus are distinctly visualized as well as the various conditions in the cardiac chambers during the cardiac cycle and also its relationship to the circulation in the efferent vessels of the foetus.

Meeting, Dec. 9, 1949.

*L. Rüdbeck: Demonstration of New Respirator.*

*T. Möller: On the Treatment of Nephrosis With Dengue Fever.*

*C.-G. Herdenstam: The Droptonator and Its Clinical Usage.*

An apparatus for optic and acoustic registration of the drop rate in intravenous drip transfusion is described. When used in heart catheterization both signals are released as the drop falls into the drip chamber. When used in common intravenous drip transfusion each drop produces an optic signal, but a continuous acoustic signal is obtained if the drop flow becomes blocked.

*A. Lichtenstein, T. Caspersson, and B. Thorell: Thrombocyte Examinations in Thrombasthenia. Preliminary Report.*

Report of examinations by Caspersson's method of the thrombocytes of two sisters with thrombasthenia, probably of the Glanzmann or Naegeli type. Result: in absorption curves for these cases the ratio between nucleotide content and cyclical amino acids in the thrombocytes was less than  $1/10$  of the lowest values observed in normal individuals. Patients with other bleeding diseases, haemophilia, thrombocytopenic purpura and purpura without thrombocytopenia, show normal or almost normal values.

Thus in the thrombasthenia cases there was present a pronounced lowering of nucleotide content of the thrombocytes, in comparison with normal conditions. As nucleotide metabolism is intimately related to the albumin metabolism this suggests a strong disturbance of one of the central functions of the thrombocyte.

*A. Lichtenstein: On the Spastic Problem.*

Spastic children are not treated in a satisfactory manner in Sweden, whereas in Anglo-Saxon countries particular interest has been directed to this group of children. Among other things, it has been observed that mental backwardness is often not so great as appears at first sight and even after ordinary testing, and that the results of systematised treatment may be much better than was previously thought.

The treatment given at present to spastic patients in our country is both gymnastic and to a certain extent psychological. The gymnastic treatment is often started too late, however, and the same applies to the psychological. The lack of suitable treatment centres for chronically sick children is certainly a contributory cause of this unsatisfactory condition.

Drugs such as prostigmine and curare may have a certain amount of sustaining effect in treatment. At Kronprinsessan Lovisa's Children's Hospital a tridion resembling the Swiss preparation Parpanit was tried and appears promising, as it seems capable of counteracting the increased muscular tension and the athetoid movements which so often disturb the patient.

I have proposed to the Swedish Red Cross National Committee that a trial be undertaken under the direction of the Red Cross in a small home for spastic children. The aim would be to start gymnastic and psychological treatment as early as the first year of life, in the hope of achieving maximum development of motoricity, counteracting contractures and wrong postures and stimulating mental development.

*Bernhard Landtman: Arrhythmias of the Heart Mechanically Produced.*

Up to now heart catheterisations have been performed on about 150 children at Kronprinsessan Lovisa's Children's Hospital, chiefly with the object of diagnosing congenital heart defects. No complications of clinical significance have occurred. Nevertheless, on careful electrocardiographic recording of the heart's action during the various phases of catheterisation it was found that transitory disturbances of the heart's action arose in almost every case. None of the patients displayed spontaneous arrhythmia prior to or after catheterisation. The transitory disturbances represented practically all forms of arrhythmias in children and adults, such as ectopic contractions, tachycardia, ectopic rhythms, auricular flutter and irregularities arising as a result of disturbances in the reflex channels.

The great majority of these disturbances were recorded when the catheter tip touched the infundibulum between the pulmonary artery and the right ventricle and the tricuspidalis region. The observation seems to demonstrate that the peripheral branches of the specific muscle system are most likely to give rise to ectopic irritation.

The observations show that the heart arrhythmia's pathogenesis is not specific, seeing that the same irritation of the endocardium can give rise to various disturbances both in the reflex channels and in the creation of irritation. The same mechanical irritation of a restricted area of the specific muscle system can also produce ectopic contractions proceeding from other parts of the heart, even those located on the other side of septum.

*Birger Broman: Rh-Immunization of Rh Positive Mothers.* (Publ. in Nord. Med. 43: 218: 1950.)

In a survey of 250 Rh immunized mothers examined during the past two years it was found that 5 of them (2 %) were Rh positive. The Rh antibodies found in the serum of these Rh positive mothers were 2 anti C<sup>w</sup> (anti Rh<sup>w</sup>), 1 anti E (anti Rh'') and 2 anti c (anti hr'). The children of all 5 showed a picture of erythroblastosis fetalis and only one survived the second day of life.

It is pointed out that in cases of suspected erythroblastosis fetalis or hemolytic blood transfusion accidents when the mother or the recipient is known to be Rh positive, this knowledge alone should not be considered sufficient to rule out possibility of an Rh immunization. In such cases a more detailed Rh investigation should be made.

Meeting, Feb. 10, 1950.

*A. J. W. Hagströmer: The Significance of the Mother's Age for the Occurrence of Cheilognathopalatoschisis.*

From observation of Stockholm material the author has demonstrated an increase in the frequency of malformation at the age of c. 23 years and at 34 and over  $\left(P = 0.056 = \frac{1}{179}\right)$ .

As the author observed the same tendency in similar material from Copenhagen, it would seem justifiable to regard the said increase in frequency as statistically significant.

*Erik Frisell: On the Bifidum-Stimulating Capacity of Mother's Milk.*

In order to ascertain the effect of boiling of mother's milk on the bifidum flora in the infant's intestine the author: 1. Compared the bifidum flora in breast-fed children and children brought up on boiled mother's milk; 2. Carried continuous investigation of the bifidum flora in children changed over from unboiled to boiled mother's milk and vice versa.

The investigation showed that the number of Bact. bifidum in the faeces of infants aged 10 days—3 months is appreciably lower if the

child receives boiled mother's milk instead of unboiled. The investigations confirm the assumption long made that there exists a bifidum-stimulating factor in mother's milk. They show that this factor is thermolabile and destroyed by boiling (short heating up to 100° C). This circumstance had not previously been shown. It constitutes further evidence that mother's milk when boiled loses some of its natural properties. It has long been known that this involves evident disadvantages to the child. Nevertheless, it is not yet clear what role *Bact. bifidum* plays in the infant's organism. Consequently the question as to the manner in which the child suffers when the bifidum flora in the intestine is reduced to  $\frac{1}{10}$  of the natural value must be left unanswered. Moreover, the bifidum-stimulating factor does not seem to constitute a necessary condition for the thriving of *Bact. bifidum* in general in the intestine. If the mother's milk is boiled the pH of the faeces is not changed, however, despite the sharp decrease in the bifidum flora. This speaks against the theory that the low faeces pH of the breast-fed infant may be due to its special bifidum flora.

**G. Laurell: Epidemic Dyspepsia in Infants.**

Investigations have been carried on at the Sachs Children's Hospital since September, 1949, concerning epidemic dyspepsia in infants, particularly as regards the existence of *Bact. coli neapolitanum*. Altogether 246 children have been treated at the hospital. Of these, 196 children constituted the control group, while 49 were children treated for epidemic dyspepsia in whom *B. coli neapolitanum* were demonstrated. All the children with dyspepsia were under 1 year and 12 of them were suffering from debility. It is specially interesting that *B. coli neapolitanum* could be demonstrated not only in the faeces but also in the throat or nose in no fewer than 25 children. This would seem to indicate that *B. coli neapolitanum* is an air-borne infection. When the surroundings were examined *B. coli neapolitanum* was found in the air but not in milk or on nipples, thermometers etc. The staff were continually subjected to control and two nurses and one doctor were bearers of *B. coli neapolitanum*. One of the nurses suffered with diarrhoea in conjunction with this. In the treatment streptomycin was tried first but without any specific therapeutic effect. As the species proved to be susceptible to aureomycin, only this antibiotic was used subsequently. Definite effect was obtained with aureomycin. Even after a short period of treatment it was no longer possible to find *B. coli neapolitanum* either in the faeces or the respiratory channels. Parallel with this bacteriological result there was a clinical improvement in the cases treated.

**E. Hagberg: Clinical Testing of BCG Tuberculin.**

BCG tuberculin was produced and tried out in 1945 in accordance with an idea of Magnusson and in close collaboration with Lithander at

the State Bacteriological Laboratory in Stockholm. It is prepared from BCG cultures and following careful experiments on animals has been tested clinically at the Sachs Children's Hospital. It has been found that in Calmette vaccinated infants an appreciably earlier and surer tuberculin positivity is obtained with this tuberculin than with ordinary standard tuberculin and thus that a specific immunity is formed in many cases before the intracutaneous test with 1 mgr standard tuberculin shows a positive reaction. An account is given of investigations carried out during 1949 comprising more than 2 000 infants. The difference between the two sorts of tuberculin stands out even more clearly in older children (1—7 years), 80 % of whom are positive 3 weeks after Calmette vaccination with the BCG tuberculin.

Meeting, March 19, 1950.

**G. Lindberg: Aureomycin Treatment of Herpes Zoster and Varicella.**

**G. Herlitz: Stevens-Johnson's Syndrome and Malignant Bovine Catarrhal Fever.**

In connection with the discussion of a possible virus aetiology in erythema exudativum multiforme (Stevens-Johnson's syndrome), reference is made to the occurrence in cattle of a syndrome, malignant bovine catarrhal fever, in which the clinical and pathological picture agrees in detail with Stevens-Johnson's syndrome in human beings and in which the picture can be reproduced in other cattle by transfer of blood from the affected animals in the high fever stage. Two cases of the syndrome in children in Östergötland are related where agreement in time and place with a case of malignant bovine catarrhal fever was such that something more than pure coincidence could be believed to exist. (Published in greater detail in *Nordisk Medicin*, 1950.)

**Bengt Hagberg: Two Cases of Guillain-Barré's Syndrome in Children.**

The syndrome's characteristic features are first surveyed. Two cases at the Children's Hospital in Linköping are related, one being a girl 4 1/2 years old and the other a boy of 1 year 10 months. In both cases there were typical symptom pictures, with slack symmetrical paresis of the trunk and extremities, absence of muscle reflexes, pronounced tenderness of muscles, albuminocytological dissociation, alternate progression and regression, afebrility and complete restitution in 2 and 4 months, respectively. In addition there were observed engagement of the cranial nerve musculature in the form of one-sided facial paresis, with slurring speech in the girl and gum paresis in the boy. In conclusion, clinical features of importance for differential diagnosis from poliomyelitis are stated.

*Brita Mannerheim: Five Cases of Dermatomyositis From the Children's Hospital at Linköping.*

The first case was observed in 1930, the second in 1948 and the other 3 in 1949. All had the characteristic tenderness in the musculature with deteriorated rough force and 4 had contractures with pointed foot or restriction of abduction in the thigh muscles. Biopsy of the muscle was performed in 3 of the later patients. Positive reactions were obtained in 2 cases; in the third, where typical skin and muscle symptoms were present, biopsy was not tried until late in the course of the disease, when it was just dying down. Skin symptoms in the anamnesis of 4 of the cases were interpreted as measles or drug exanthema. In the later course of the disease 3 of these 4 had the typical blue-red butterfly-form erythema with oedema in the face. All the cases had subfebrile temperature and moderately raised blood S. R. Four of the cases had eosinophilia, one up to 27 %. One of the patients was 11 years old, three were 4 and one was 3, that is younger than the age of predilection, stated to be 13—16 years. The first 4 cases became free of symptoms without any specific treatment. On the last patient, still in hospital, PAS, paraminobenzoic acid, nicotine acid amide and antihistaminotica have been tried without result. A certain improvement has been noted, however, viz: afebrility and lowered S. R., in this case after implantation of calf hypophysis. Pending receipt of ACTH, trials have been made with doea and injections of C-vitamins started.

*S. Mårtensson: Case of Epidermolysis Bullosa Hereditaria.*

A case of Epidermolysis bullosa hereditaria was demonstrated. Initially the course was rather malignant with abundant blister formation and a slow increase in weight. One of the patient's brothers had died on the tenth day after birth with a disease picture that corresponded to the third form of the disease as presented by G. HERLITZ in 1935, the lethal form. It was therefore expected that the course of the present patient's disease would be unfavourable, with death within a few months. But the patient has so far survived and developed normally, weighing 9 720 g at 12 months; whereas cases of epidermolysis bullosa hereditaria lethalis previously described in the literature have succumbed after not more than 7 1/2 months. The author considers the explanation of the patient's long survival to be that he received from the beginning strong prophylactic treatment with antibiotics (penicillin) and later chemotherapeutica (sulphadimine), which prevented secondary infection via the skin defects. Moreover, albumine losses from the evacuated contents of the blisters was compensated for by amino acid therapy (aminosol per os).

Meeting, April 14, 1950.

**M. Bohman: Periarthritis Nodosa in an Infant Aged Three Months (Effect of Whooping Cough Inoculation?)**

**H. Wingstrand: Case of Acute Haemolytic Anaemia in a Two Year Old Girl; Treated With Exchange Transfusion.**

A two year old girl in poor condition was admitted to the hospital displaying all indications of an acute haemolytic anaemia of Lederer type. She was extremely icteric with an icterus index of 1: 65, hgb 3.6 %, RBC 910 000. Haemoglobin was demonstrated in the urine, which was cherry red. In spite of repeated blood transfusions totalling 1 000 ml in the course of a few days there was no noticeable improvement, so reciprocal transfusion was undertaken. Immediately thereafter normal blood values were obtained and the icterus and haemoglobinuria disappeared within six days. The blood values have since remained stable throughout an observation period of several months. The aetiology is unknown, but the patient had a haemolytic streptococcus infection in the throat which may have been a contributory factor.

**Elias Bengtsson: Bundle-Branch Block in Children.**

A survey of previously published cases of bundle-branch block in the earlier ages reveals that no total obstructions in children have hitherto been reported. Thanks to a number of new examination methods, particularly Wilson's unipolar leads, vectorcardiography and electrokymography, interventricular obstructions can now be diagnosed better than formerly. — A survey is made of the electrocardiographic classification of bundle-branch blocks and the author points out the difficulty of differentiating atrioventricular and interventricular obstructions when a lesion affects both limbs equally. Reference is made to STENSTRÖM's work.

The author's own series includes cases selected from among 4 000—5 000 patients treated at the Hospital for Contagious Diseases during the period April—Dec. 1949. There was cases of complete, partial and focal bundle-branch block in children. Certain ones had definite connection with myocarditic processes; others were familial or constitutional. Isolated instances were affected by vegetable drugs. In all no less than five total obstructions were observed; there was an approximately equal number of other types. Two of the first-named were familial. They were followed over a 6—12 month period. One of the total obstructions occurred in the course of a morbilli infection and gave clinical signs of cardiac decompensation.

**DISCUSSION: Maj Levander-Lindgren:** Among the series of 3 000 scarlet fever cases from the Stockholm Hospital for Contagious Diseases 1946—



49 which I reported here a year ago, and which is soon to be published in detail, there were several with continual interventricular obstruction and 2 with intermittent bundle-branch block. Both were boys aged 2 and 3, respectively, without clinical cardiac symptoms. Routine ECG examination revealed atypical right-sided bundle-branch block, Wilson block, width 0.10–0.11", alternating with normal ventricular complex. P–Q interval always normal and constant. One of the children was checked after three years and at that time showed good functional capacity on the cycle ergometer and normal ventricular complexes on resting and working ECG tracings. The other boy has shown the same picture throughout a five month observation period. At higher frequencies the pathologic and at lower frequencies the normal ventricular complexes have been dominant.

*Justus Ström: Penicillin Per Os in Scarlet Fever, Particularly From the Bacteriologic Point of View.*

The author reports on experiments with peroral penicillin treatment in scarlet fever, particularly from the bacteriologic point of view. Comparison is made with simultaneous penicillin procaine treatment.

In the first experimental series 20 000–100 000 I.E. (depending on age)  $\times$  3 penicillin in glucose solution was administered per os in alternate cases; the other cases were treated with 50 000–150 000 I.E.  $\times$  1 penicillin procaine. Of the 255 cases who received the first treatment 211 (82.7 %) were negative in tests taken on three successive days after six days' treatment. The corresponding figures for penicillin procaine were 238 (91.5 %) out of 260 cases. During the nursing period (three weeks) there was a recurrence of streptococci in 31 % and 16.5 %, respectively, and these had to undergo renewed treatment. One week after discharge 15.5 % and 8.3 %, respectively, were positive again.

In the second experimental series the doses were increased to 40 000–150 000 I.E.  $\times$  3 for penicillin per os and 75 000–200 000 I.E.  $\times$  1 for penicillin procaine. Of the 195 cases with the first treatment 86.2 % now became negative after six days and of the 190 cases treated with penicillin procaine 93.7 %. In 47 (24.1 %) and 26 (13.7 %), respectively, there was a recurrence of streptococci during the three week hospitalization period. One week after discharge 16.6 % and 6.2 %, respectively, were again positive. From the bacteriologic point of view the result was somewhat better.

After short-term treatment over a six day period was introduced in uncomplicated cases in 1950, the author began to experiment with peroral penicillin in 50 000 I.E. tablets, dosage 50 000–150 000 I.E.  $\times$  3, and penicillin procaine as in the immediately preceding series. Analysis of the penicillin concentration in the blood after the first tablet was carried out in 49 cases. A concentration of c. 1 I.E./ml was obtained after half

an hour in 6—7 year olds and a lower concentration with increasing age, down to c. 0.5 I.E./ml, in the oldest group ( $> 15$  years). After four hours the mean concentration was still at a satisfactory level (0.23 I.E./ml). The blood-penicillin values obtained should be effective, since the haemolytic streptococci are remarkably sensitive to penicillin. Of 597 strains from Stockholm scarlet fever patients examined during the years 1946—48, 589 were thus sensitive to only 0.03 I.E./ml, and 8 to 0.06 I.E./ml.

In both these series of 190 cases each there was a recurrence of streptococci after at least one negative test once in 16 cases and more than once in 11 cases or a total of 27 (14.2 %) in patients treated with penicillin tablets. The corresponding figures for the penicillin procaine series were 15 and 4, a total of 19 cases (10 %). The hospital period amounted to 12.0 and 10.0 days, respectively. One week after discharge 15.2 % and 6.0 %, respectively, were positive again.

It is possible to employ penicillin per os in the treatment of scarlet fever. The clinical effect with respect to preventing complications has been good, as with penicillin procaine. The bacteriologic effect has been poorer. One week after the patients' discharge the streptococci returned two and one half times as often as after penicillin procaine treatment. This circumstance had no noteworthy significance from the point of view of danger of contagion, however. Its significance to the patients themselves with regard to later complications and above all relapse is another matter which will be taken up later. The results of our investigation of these factors will be decisive in forming our attitude both to short-term treatment as a whole and short-term treatment in peroral form.

*Per Hedlund and Rolf Lundström: Penicillin Prophylaxis During the Scarlet Fever Epidemic.*

During the scarlet fever epidemic in Stockholm in the Autumn of 1949 attempts were made to reduce the number of haemolytic streptococci carriers by means of penicillin treatment. Clinical examinations at the Stockholm Hospital for Contagious Diseases revealed that the dose, a penicillin tablet of 200 000 units, which was later used in the main experiment, gave a therapeutically active blood concentration for at least four hours. Children aged 3—14 with scarlet fever or tonsillitis who were under care at the Hospital for Contagious Diseases became free of haemolytic streptococci when they were given one such penicillin tablet morning and evening on an empty stomach. Ordinarily these patients could be discharged after one week. In these experiments both penicillin aluminium and penicillin procaine were used in the tablets. These definite types of penicillin had the same clinical effect and gave the same blood concentration.

The main experiment was made with children from the Katharina Elementary School in Stockholm. Two hundred and thirty two children aged 7—8 in the first and second grades of a school with a high scarlet fever incidence were examined for haemolytic streptococci. Thirty six per cent were carriers. Half of the pupils examined, the tablet group, were given one penicillin tablet of 200 000 units morning and evening on an empty stomach for one week. The other half, the control group, received no treatment. The penicillin treatment rid the pupils in the tablet group of haemolytic streptococci. The results were demonstrable up to a month after the conclusion of treatment. The danger of contagion was less in the tablet group than in the control group. During treatment and for c. two weeks thereafter the number of absences due to upper respiratory passage infection was less for the tablet group than for the control group. Prophylactic treatment with sulfa drugs compared with corresponding treatment with penicillin is discussed. The danger of oversensitivity in persons who have received prophylactic penicillin treatment is pointed out. The danger of inducing penicillin-resistant bacteria strains is particularly emphasized.

*E. Bengtsson, G. Birke and H. Wingstrand: The Frequency of Myocarditis in Scarlet Fever and Certain Other Haemolytic Streptococcus Infections.*

Three thousand sixty nine cases of scarlet fever were investigated to determine the frequency of myocarditis. One hundred twenty seven cases of myocarditis, or 4.14 %, were found, of which 118 were in children under 15 (3.97 %) and 9 in adults (9.0 %). From a simultaneous investigation of the frequency of myocarditis in other streptococcic infections the following preliminary report may be made. In tonsillitis with haemolytic streptococci in the throat 23 cases of myocarditis were observed out of 412. In part this series was specially selected, however; hence the frequency of myocarditis is not directly comparable. The results obtained from directly comparable series will be published later. In 313 cases of clinically healthy patients with haemolytic streptococci in the throat without an earlier streptococcic tonsillitis only 1 case of myocarditis was observed.

Meeting, June 3, 1950.

*Dr. Ragnar Berfenstam: Zinc — a Tracing Substance of Biological Significance.*

The total amount of zinc in the body equals that of iron. Likewise, approximately as much zinc as iron forms part of the food. The quantity of copper in the food is considerably less. In the blood, the greatest part

of the zinc will be found in the blood corpuscles. In the serum, the zinc occupies the same level as the iron and copper. In healthy adults, the serum zinc is, apparently, constant. Values deviating from the normal are to be found only in pregnant women and newborns. Thus, in pregnancy, the value of the serum zinc, like that of iron, is low, while being high in newborns.

The zinc in the serum can be regarded as a transport zinc. The zinc in the blood corpuscles forms part of the ferment of carbonic anhydrase which catalyzes the carbonic acid metabolism. The fermentation during the newborn stage falls below that of any other physiologic condition and is particularly low in prematures. Several authors report attacks of cyanosis in such children, in connection with the low fermental activity. The present author has shown (1949) that the zinc in the blood corpuscles in prematures, as well as in fully developed newborns, is low, and that a certain proportionality between the content of zinc and the fermentation can be perceived. The fermental activity in children can be temporarily increased by injection of blood or plasma from adults. Should this low fermental activity be contingent to a low content of zinc, i.e. a deficiency of zinc, an increase of the content of ferment should, however, preferably be attempted by means of zinc medication.

In the course of 10 weeks, a series of rabbits, by a daily peroral administration of zinc, were kept on a level of plasma zinc 10—20 times above the normal. Yet, this failed to produce any increase in the zinc content of the blood corpuscles. The same high level has been achieved in pregnant rabbits during the whole period of pregnancy, without any change in the zinc of the blood corpuscles in their offspring. Considerable amounts of zinc have been administered to these female rabbits, also when suckling. A high content of zinc has then been found in the milk, as well as in the plasma of their young though, still, no increase in the zinc of the blood corpuscles of the latter has occurred, other than that ascertained in the controls.

If a parallel with Man should be ventured upon, from these animal experiments, there may, perhaps, be justification for supposing that *no possibility exists to increase the content of zinc in the blood corpuscles by means of extra administrations of zinc.*

#### *A. Gyllensvärd: Continuous Recording of Temperature in Children.*

According to present conceptions, the variations in muscular activity constitute the only cause of changes in temperature in healthy persons over a 24-hour period. Preliminary results from continuous thermoelectric temperature registrations in children of various ages, including also prematures, appear to show that an endogenous 24-hour rhythm distinguishes the body temperature. This rhythm can be ascertained in normal newborns even during their first weeks, reaching its full develop-

ment in the second year of life. In prematures, the rhythm is noted as soon as they have become capable of maintaining the temperature without any thermogenics.

*Lars Söderhjelm: The Intestinal Absorption of Fat in Prematures.*

The fat absorption was determined by balance tests in 22 prematures fed with breast milk. Generally, it proved to be extremely good, with a mean value of 92 per cent of ingested fat. In 3 cases the absorption fell below 80 per cent, during one test period for each. Whether the milk was fresh, pasteurized, boiled or frozen did not affect the fat absorption. An addition of vegetable lecithins did not improve fat absorption in prematures, but increased it in a case of celiac disease. Peroral administration of bacteriostatic agents did not influence the excretion, or absorption, of fat.

*O. Melander: A Demonstration of Electrophoretic Apparatuses Designed for small Amounts of Blood.*

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Vol. XXXIX. Fasc. 6

1950

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1951

# ACTA PÆDIATRICA

EDITOR PROFESSOR A. WALLGREN

NORRTULLS SJUKHUS,

NORRTULLSGATAN 14, STOCKHOLM

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## Gram-Negative Staining of Gram-Positive Intestinal Bacteria with Particular Reference to Examinations of Faeces in Infants

by

CURT STÅHL and ERIK OLSEN

In a recently published investigation of the intestinal flora of infants one of us (1) has found that in both breast-fed and bottle-fed infants the predominant bacteria are *Bact. bifidum*, enterococci and *Bact. (Esch.) coli*. These bacteria are present in almost the same numbers in the two types of children. Owing to the neutral or slightly alkaline reaction of the intestinal contents of bottle-fed infants these furthermore harbour rather great numbers of clostridia, micrococci, corynebacteria and veillonella. These types of bacteria are suppressed by the acid reaction of the intestinal contents of breast-fed infants.

It was concluded that the difference in pH and odour between the faeces of bottle-fed and breast-fed infants is due to the type of food received, while the relatively small differences in the bacterial flora is a secondary reaction depending on the variation in pH of the intestinal contents. The bacteria apparently have no influence on the character of the stools.

These results, which were obtained by cultural methods of investigation, are in strong contrast to the results obtained by most other workers in this field. Thus the general opinion is that the acid-forming, gram-positive *Bact. bifidum* is found in almost pure culture in breast-fed infants, hereby bringing about the acid reaction of the stools, while in bottle-fed infants a gram-negative flora is strongly predominant.

However, most of the studies leading to this conclusion were performed by direct microscopic examination of gram-stained smears of the faeces. In the above mentioned work by Olsen this method was also compared with cultural methods.

It was found that gram-stained smears of stools from bottle fed infants contained 50-100 times as many gram-negative as gram-positive cells, while the proportion was far smaller in breast-fed infants. Furthermore a fair agreement was found between the number of gram-positive cells in the smears and the number found by platings on different media. Only in exceptional cases were there more than two or three times as many gram-positive bacteria in the smears as on the substrates; frequently the two findings were in complete agreement.

As is well known the major part (about 95 % (2)) of the bacteria in the faeces are dead, and the discrepancies between the results arrived at in the two methods of investigation must undoubtedly be ascribed to the fact that the majority of the dead gram-positive bacteria rapidly become gram-negative.

As similar observations have not — as far as we have been able to trace — been reported in the literature, and as they may be of interest in future studies, e. g. in later successful attempts to treat certain intestinal disorders by changing the intestinal flora by means of lactic acid bacteria (RETTGER a.o.), we have considered it of interest to examine the stability of gram-positive intestinal bacteria against gram-staining.

### Present Investigations

The idea of examining the effect of the most important digestive secretions, viz. the bile, the pancreatic enzymes and the pepsin, quite naturally suggested itself as they are all, so to speak, added in the first part of the intestine, and are consequently able to act throughout its length. As far as pepsin is concerned, one would hardly expect any very significant effect to be produced by the reactions which are predominant in the intestinal tract, with the exception of its first portion, in which the reaction is still weakly acid, for which reason the possibility of a certain

effect of pepsin on the staining properties of the bacteria cannot be excluded a priori. The following bacteria were available for our investigations: *Thermobacterium lactis*, *Thermobacterium intestinale* (= *Lactobacillus acidophilus*) and *Streptococcus faecium*, all of which occur in breast-fed as well as in bottle-fed infants, and also *Bacterium bifidum*, which is often said to predominate in breastfed children.

The experiments were carried out in vitro and the procedure was as follows. The said bacteria were first cultivated for 24 hours in a test tube with 10 ml. of casein-peptone bouillon to which had been added 25 % yeast autolysate (with  $\frac{1}{2}$  % nitrogen) and 1 % dextrose; when *Bacterium bifidum* was being examined, 1 % ascorbic acid was also added. The pH was 6.7. The bacteria were then killed by heating to 80° C for 10 minutes, as our investigations, as already mentioned, were limited to the staining properties of the dead bacteria. When the solution was cool the bile and the enzymes were added, and finally the tubes were adjusted to the desired pH with n/4 solution of hydrochloric acid or sodium hydroxide. pH values between 8 and 5 were decided upon as corresponding to the reactions occurring in the intestine. Samples for assay of the gram-staining properties of the bacteria were drawn from the tubes on the same day, after 24 hours and after 48 hours. The tubes were left from one day to the next at 37° C; the pH was checked daily and showed only insignificant variations. The bile used in the experiments was of human origin; it was autoclaved and added in the ratio 1 : 10. The enzyme solutions were freshly made of pancreatin "Rhenania" and of pepsin (strength 1/5000) by dissolving 1 g of the material in 20 g of water; this solution was filtered through a Seitz filter and added to the tubes, likewise in the ratio 1 : 10, giving the substrate an enzyme content of 0.5 %.

The technique employed in the drawing of samples was as follows. After shaking the test tube vigorously 2 loop-fulls of the material were withdrawn and smeared evenly on a flamed slide so as to cover an area measuring 0.5 × 1 cm. After having dried in the air the preparations were fixed in the flame and gram-stained carefully according to the following schedule.

- 1) Staining: 1 % of aqueous solution of crystal violet for one minute.
- 2) Iodine treatment: a solution of iodine in potassium iodide (1 : 2 : 100) for two minutes.
- 3) Decolourisation: Shaking gently with 96 % alcohol for 15 seconds, followed by a quick wash with water.
- 4) Counterstaining: a 0.1 % aqueous solution of carbol fuchsin for one half minute, washing with water.

The countings were done lengthwise through the slide after we had made sure [by low-grade magnification] of the uniform distribution of the bacteria. About 50 fields were counted with oil immersion objective and there was good agreement between parallel preparations except in a number of preparations containing *Sc. faecium*, which were therefore left out.

### Experiment I

First of all we wanted to ascertain to what extent the heat killed *Tbm. lactis* have a tendency to spontaneous loss of the gram-positivity under the conditions of our experiments. For comparison, simultaneous experiments were carried out with bacteria killed with chloroform (10 drops of chloroform in each tube). The results are listed in Table I.

Table I

Organism	Number of Tubes	pH	Mode of Killing	Gram-Positive %			
				Same Day	After 24 hrs	After 48 hrs	After 72 hrs
<i>Tbm. lactis</i>	5	8-7-6- 5-4	80° in 10 min.	98-95-92	97-96-92	89-74-63	75-56-33
	5	8-7-6- 5-4	chloro- form.	100-100-99	100-96-83	95-85-73	79-70-55

The figures in the table show the highest and the lowest value obtained in countings of the five tubes, the figure in the centre giving the average of the five countings. The pH appeared to be of no significance in this or in any of the subsequent experiments. Experiment I shows that in heat-killed bacteria as well as in those killed with chloroform a declining gram-positivity is not in evidence till after 48 hours; it is most pronounced, however, in the heat-killed.

### Experiment II

In the next experiment we wanted to examine the effect of bile and enzymes, partly separately, partly jointly, on *Tbm. lactis*, *Bacterium bifidum* and *Sc. faecium*. The results are shown in Table II.

Table II

Organism	Number of Tubes	pH	Addition of			Gram-Positive %		
			Pan-creatin	Pepsin	Bile	Same Day	After 24 hrs	After 48 hrs
<i>Tbm. lactis</i>	4	8-7-6-5				98-94-92	97-96-95	89-71-63
	4	"	+	+	+		85-81-77	52-28-5
	4	"	+				85-84-81	74-57-29
	4	"		+			96-85-73	73-62-43
	4	"			+		88-83-79	74-69-65
<i>Bact. bifidum</i>	4	8-7-6-5				100-100-100	99-99-97	100-94-90
	4	"	+	+	+	68-59-46	83-74-65	71-51-29
	4	"	+			100-100-100	96-78-60	4-3-0
	4	6-5-4-3		+		100-99-99	99-84-60	74-57-29
	4	8-7-6-5			+	100-79-60	95-85-66	98-94-89
<i>Sc. faecium</i>	4	8-7-6-5				100-100-98	98-94-90	91-83-67
	4	"			+	100-99-98	98-91-82	100-99-90

Table II shows a slight effect after 24 hours in all the tubes containing *Tbm. lactis*, and a considerable change in the direction of gram-negativity after 48 hours in the tubes containing enzymes + bile. The effect of each enzyme is slight and the bile has no effect.

In the experiment with *Bact. bifidum* a slight effect is likewise demonstrable in all tubes after 24 hours; after 48 hours there are almost exclusively gram-negative bacteria in the tube with pancreatin. There was also a definite effect from pepsin alone and from the combination enzymes + bile. In this experiment, too, the bile had no effect except on the day of the experiment, and this effect subsided during the following days. The experiment with *Sc. faecium* also showed that bile alone is without any effect. The other preparations of this bacterium did not lend themselves to counts, but many gram-negative bacteria were observed in several of them.

## Experiment III

In a last experiment we wanted to check the previous results, and in view of the fact that enzymes and bile always coexist in the intestine under normal conditions we decided to limit our investigation to this combination. The results is presented in Table III.

Table III

Organism	Number of Tubes	pH	Addition of			Gram-Positive %		
			Pan-creatin	Pepsin	Bile	Same Day (without bile and enzymes)	After 24 hrs	After 48 hrs
<i>Tbm. lactis</i>	4	7.5-5.5	+	+	+	98-89-77	51-46-43	41-32-16
	4	" "				83-80-75	90-79-69	71-59-49
<i>Tbm. intestinale</i>	4	" "	+	+	+	99-96-92	75-42-11	80-68-47
	4	" "				99-98-96	91-75-68	94-80-58
<i>Bact. bifidum</i>	4	" "	+	+	+	99-96-95	79-66-51	36-28-19
	4	" "				100-96-91	90-85-82	74-66-58

The table affords unambiguous confirmation of the results of the previous experiments.

Our results show that under the conditions of our experiments the mixture of pepsin, pancreatin and bile has such an effect on the gram-positive bacteria studied that they start becoming gram-negative within 24 hours. The increasing gram-positivity exhibited by *Tbm. intestinale* in Experiment III from the twenty fourth to the forty eighth hour may presumably be ascribed to the bile; the control tube also presents, however, a slight rise of which we are unable to give any explanation.

It was particularly interesting to observe the bacteria changing from gram-positivity to gram-negativity. *Tbm. lactis* and *Tbm. intestinale* appear to change their colour gradually from the dark blue of gram-positivity via pale blue and violet to the gram-negative red. The colour changes first at the ends of the bacterial chains. *Bacterium bifidum* initially presents itself as almost



black, partly club-shaped, rods which gradually decrease in size and become purely rod-shaped with almost tapering ends whence the red colour starts displacing the bluish-black. The red colour extends like a brim along the cell membrane, penetrating into the protoplasm at the centre of the bacteria. This gives the remaining, vigorously gram-positive stained portion of the bacterium a close resemblance to diplococci. In a few instances such "cocci" are also observed without the gram-negative staining. The entirely gram-negative bacteria look like rods. In the case of *Sc. faecium* intermediate forms occur in which the cell as a whole is gram-negative, presenting a gram-positive brim between the protoplasm and the cell membrane near the poles of the oval coccus. Other authors have in experiments with reversible decolourisation of gram-positive bacteria observed that the decolourised bacterium is again becoming gram-positive in a system of "Kondensations-Kernen".

### Discussion

Although more than 60 years have passed since the Dane C. Gram arrived empirically at his staining method which, by dividing bacteria into two large groups, has obtained such a central position in bacteriology, we do not yet know for certain which factors are responsible for their staining properties. Some investigators have attached a decisive importance to the protoplasm proteins and their ampholytic properties (STEARNS & STEARNS).

The isoelectric point of the gram-positive bacteria thus lies about pH 2 and they are stainable with alkaline dyes such as crystal violet at reactions which are alkaline in relation to this level (4). As our examinations were carried out at pH levels ranging from 8 to 5, which is on the alkaline side of pH 2, this would seem to offer an explanation of the fact that we have been unable to observe any influence of the chosen reactions, which correspond to those occurring in the intestinal tract. Other theories indicate the lipid contents of the bacteria or the structure of the cell membrane to be the decisive factor.

HENRY & STACEY (5) showed that the salts of bile acids are able to render certain bacteria, e.g. *Clostridium welchii*, gram-

negative, but reversibly, as the magnesium salt of ribonucleic acid restores to them their normal gram-staining properties. From this finding they drew the conclusion that the absence of the said salt is responsible for the fact that bacteria in old cultures become gram-negative. It has in addition been proved (6) that ribonuclease renders heat-killed staphylococci, lactobacilli and clostridia gram-negative. In our experiments we have likewise found a reversible effect of bile which in this case, too, may possibly be attributed to the presence of bile salts; we have, however, no knowledge about the presence of magnesium ribonucleate in our substrates.

The theoretical basis for the action of the enzymes must be that the cell proteins are influenced by a proteolysis which may be brought about by pepsin as well as by the trypsin of pancreatin. As far as pancreatin is concerned it would seem that an action of the lipase on the cell lipoids may also be of importance, in some cases accentuated by the presence of salts of bile acids.

### Conclusions

If gram-stained faecal smears are used in examinations of the intestinal flora of infants, it must be reckoned that only part of the gram-negatively stained bacteria belong to the coli group, while most of them presumably are decolourised gram-positive bacteria. This undoubtedly holds good particularly for bottle-fed infants in whom the apparently gram-negative bacteria are so numerous because these children have a slower intestinal passage (24-30 hours) than breast-fed infants (4-16 hours) and the enzymes consequently have a longer action time.

The fact that the clotted coagulum of cow's milk in the stomach is but slowly penetrated by the bactericidal hydrochloric acid is undoubtedly also of decisive importance. For this reason a colossal multiplication of bacteria takes place in the stomach of bottle-fed children. The death of these bacteria means that the microscopic preparations from these infants contain a larger number of bacteria upon the whole and, moreover, a much higher percentage of apparently gram-negative bacteria than do the pre-

parations from breast-fed children, in whom the flora in a higher degree is purely intestinal. The factors which have been enumerated above will bring about a highly distorted picture in a gram-negative direction, particularly in bottle-fed children, for which reason the observer will have to resort to the more complex methods of cultivation in assaying the intestinal flora in infants.

### Summary

The observation made by E. OLSEN (1) that dead gram-positive intestinal bacteria of young infants stain gram-negatively in smears of faeces is confirmed by the experiments which have been carried out in the present work. A combination of pepsin, pancreatin and bile have proved to accelerate the change to gram-negativity which occurs spontaneously in vitro in heat-killed *Tbm. lactis*, *Tbm. intestinale* and *Bact. bifidum*. A distinct effect is in evidence even within the first 24 hours. A few experiments suggest that *Bact. bifidum* is most strongly influenced by pancreatin alone, whereas the combination of enzymes and bile has the greatest effect on *Tbm. lactis*.

C. STÄHL & E. OLSEN: *Le changement en gram-négativité des bactéries intestinales gram-positives chez le nourrisson.*

L'observation faite par E. OLSEN (1) que les bactéries intestinales gram-positifs mortes forment des taches gram-négatifs dans les couches de matières fécales de jeunes enfants est confirmée par les expériences faites dans le présent ouvrage. On a constaté qu'une combinaison de pepsine, de pancréatine et de bile accélère le changement en gram-négatif qui se produit spontanément in vitro dans les *Tbm. lactis*, *Tbm. intestinale* et *Bact. bifidum* tués par la chaleur. Un effet distinct se manifeste aussi dans les premières 24 heures. Quelques expériences suggèrent que *Bact. bifidum* est plus fortement influencé par la pancréatine seule, tandis que la combinaison d'enzymes et de bile a le plus fort effet sur *Tbm. lactis*.

C. STÄHL und E. OLSEN: *Veränderung von gram-positiven Darmbakterien zu gram-negativen bei Säuglingen.*

Die Observation von E. OLSEN (1) dass tote gram-positive intestinale Bakterien in Abstrichen der Stühle von Säuglingen gram-negativ sind, wird experimentell bestätigt. Eine Mischung von Pepsin, Pancreatin und Galle beschleunigt die Veränderung der Bakterien zu gram-negativen, eine Veränderung die bei durch Wärme getöteten *Tbm. lactis*, *Tbm.*

*intestinalis* und *Bact. bifidum* auch spontan im Vitro eintritt und schon innerhalb 24 St. deutlich wird. Einige wenige Versuche deuten darauf hin, dass *Bact. bifidum* durch Pancreatin allein kräftig beeinflusst wird, während beim *Tbm. lactis* eine Kombination der Enzyme und Galle die stärkste Einwirkung hat.

C. STÄHL y E. OLSEN: *El cambio de bacterias intestinales gram-positivas a bacterias gram-negativas en referencia a la examinación de heces infantiles.*

La observación hecha por E. OLSEN (1) de que las bacterias intestinales gram-positivas muertas no tomam el gram pero mas bien tiñan gram-negativamente en las heces de niños jóvenes está confirmada por los experimentos expuestas en la presente obra. Se ha comprobado que una combinación de pepsina, pancreatina y bilis acelera el cambio de gram-positivo a gram-negativo que se produce espontáneamente in vitro en los *Tbm. lactis*, *Tbm. intestinale* y *Bact. bifidum* matados por el calor. Un efecto distinto se manifiesta dentro de las primeras 24 horas. Algunas experiencias sugieren que la *Bact. bifidum* es más fuertemente influida por la pancreatina sola, mientras que la combinación de enzymes y de bilis tiene el más fuerte efecto sobre el *Tbm. lactis*.

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Received 20.3. 1950.

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI.  
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## **On Convulsions in Early Childhood and Their Prognosis**

**An investigation with follow-up examinations of patients treated for  
convulsions at the Children's Clinic of Helsinki University**

by

**ERIK EKHOLM and KALEVI NIEMINEVA**

Convulsions appearing in connection with spasmophilia and infectious diseases in children and their prognoses have in the past been described in this periodical. The mental deficiencies which the children may have contracted from these diseases have been in the foreground for study. Of the investigators who have discussed this question we may mention HJÄRNE, NORDENFELT and HERLITZ. The recent publication of the first part of ZELLWEGER's monographs in Switzerland shows that the matter is still of interest.

Most interesting and most important from the standpoint of the practising physician are the differences of opinion as to the prognosis. The oldest publications on follow-up examinations of convulsive patients date from the early years of this century. In these works the authors came to the conclusion that only a fraction of the patients later developed quite normally. There are more recent German investigators who still adhere to this opinion (SCHOUZ, VOIGT). A different view, on the other hand, is taken by the Scandinavian writers mentioned above. HERLITZ expressly observes in the summary of his extensive investigations on initial convulsions that in these instances there is possibility of epilepsy at a later age in only a small percentage. However, he emphasizes the difficulty of drawing conclusions.

As opinions on the prognosis of convulsions are so different and as in Finland no similar research has been done, we have

thought it worth while to investigate the cases at our disposal in Helsinki Children's Clinic, keeping the prognosis chiefly in view.<sup>1</sup> Special attention has been given to sufficiently long periods of observation. As social conditions influence the state of the diseases in which convulsions appear, especially in spasmophilia, mention of the investigations performed in different countries abroad is necessary to clarify the character of convulsions under varied local circumstances.

### Own Investigations

#### Classification of Cases

The material comprises 221 children treated for convulsions at the Children's Clinic of Helsinki University during the years 1920—1941. We have taken into account all cases of convulsions except those thought to result from meningitis or encephalitis or attributed to hemorrhage in the brain of newborn infants or congenital malformation. Cases of major intelligence defects and hysteria have also been excluded. Of the epileptic patients we have included only the doubtful cases under 3 years of age. The patients attending this hospital are children whose homes are either in the city of Helsinki or in the adjoining rural districts. Of the cases under investigation 101 were from the city and 120 from the country. The material was evenly distributed among all classes of society, in our opinion in the same proportion as these are represented in our country. Concerning the follow-up examinations made abroad, for instance by NORDENSON and VOIGT, it must be remarked that the present authors understand that the subjects of their investigation belonged to the poor population of a big city.

We have divided the cases into four groups on the following basis. The first and largest group comprises the convulsions appearing in connection with infectious diseases. In this group we have included all the cases where the clinical symptoms of infection were clearly ascertained. However, cases in which symptoms of spasmophilia were apparent we classified in the second

<sup>1</sup> C.-E. RÄIHÄ, M. D., has encouraged us to make this investigation.

group, which is the next largest and comprises all the cases of convulsions associated with spasmophilia. In diagnosing spasmophilia we applied the criteria established by FEER, according to which a clear facial sign is pathognomonic for those under 2 years of age and a clear peroneal sign for those under 1 year. The TROUSSEAU sign has been considered pathognomonic for all age groups. C.O.C. gives the limit value as 5 mA, whereas the normal lower calcium limit of the blood is 8 mg%.

In the third group, "miscellaneous convulsions," we have put the cases which on the strength of the clinical picture we have not been able to place in the foregoing groups; this is because we have wanted to keep them as homogeneous as possible. We know that the cases under "miscellaneous convulsions" could belong to one of the two preceding groups.

As to the size of these groups, we have 91 cases under infection convulsions, 61 under spasmophilia and 54 under miscellaneous convulsions.

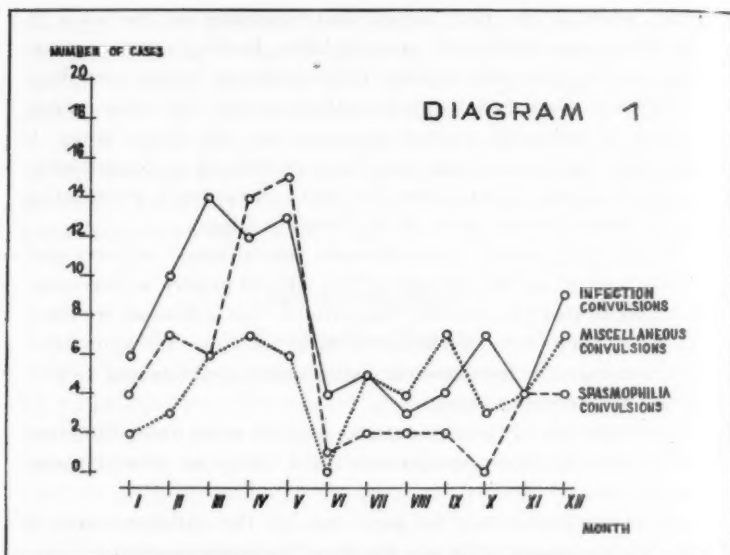
In the fourth group we have put all the children under 3 years of age treated with the diagnosis "uncertain epilepsy," but we considered that at least a part of them belonged to one of the above groups. The fourth group is much smaller than the others, including only 15 patients.

The organic diseases of the central nervous system have been excluded, mainly on the basis of the clinical picture. Lumbar puncture has been carried out in 34 patients in our series. In all these cases, among which naturally were those most suspected of organic disease, the C.S.F. findings were normal.

#### **Distribution of Cases throughout the Year**

It is a well known fact that spasmophilia occurs most frequently in late winter and in spring. This can be seen clearly in Diagram 1, where we find that most of the cases occurred in April/May, whereas in October there were none.

Infection convulsions were most common in early winter and in spring. At these periods the respiratory infections are most frequent in Finland, and as will be seen later, in our country attacks of convulsions are most usual in connection with these.



In the occurrence of miscellaneous convulsions there was hardly any fluctuation other than that at midsummer they almost disappeared.

Upon comparing the results with those obtained abroad a general agreement will be seen. An exception is the material of ZELLWEGER from the Children's Hospital in Zürich. In this cases most infection convulsions appear in the summer months, although differences between these and other months are not very clear. In spite of this summer diarrhea is no more common among the diseases in his series than in ours.

#### Sex and Age of Patients

In HERLITZ's series of initial convulsions the number of boys was proved statistically to be greater than that of girls. He considered that the reason for this phenomenon was the greater general susceptibility of boys of this age group to disease as well as their greater mortality. In his material 44.3 % were girls.



Table 1.

## Convulsions according to Sex.

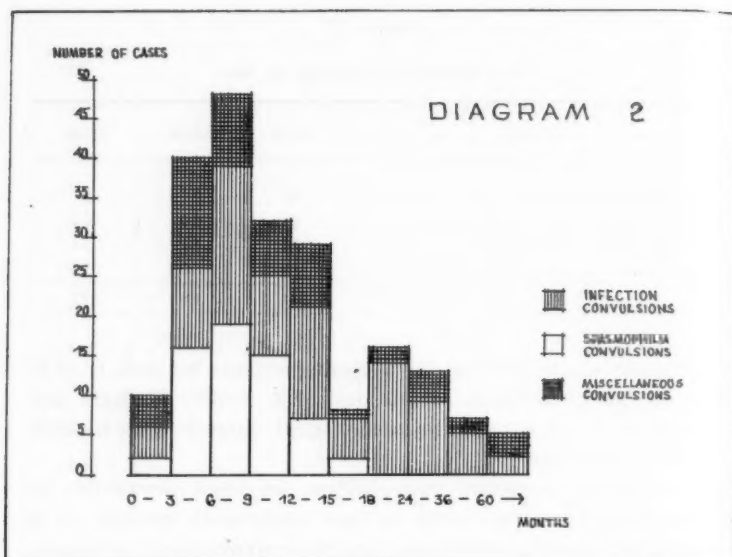
Group	Boys	Girls	Total
Infection Convulsions .....	57	34	91
Spasmophilia Convulsions .....	41	20	61
Miscellaneous Convulsions .....	34	20	54
Uncertain Epilepsy .....	9	6	15
	141	80	221

In our whole material the percentage figure for girls is 36.2; in the case of infection convulsions, 37.3. Unlike HERLITZ and ourselves, ZELLWEGER shows no numerical variance in the number of boys and girls.

PETERMAN considers that children are most susceptible to convulsions from their sixth to their thirty-sixth months. It is at this period of the child's age that the convulsions of the largest group, namely infection convulsions, predominate (48.2 %). In the extensive series of initial convulsions compiled by HERLITZ 40.5 % of the cases fall between the ages of 1 and 2 years. ZELLWEGER comes to the same conclusion. — In the material on spasmophilia examined by HERLITZ in his work on comparative study, there are none above the age of 21 months, and almost 2/3 fall within the age of 7 to 12 months. — The same is the case according to NORDENFELT in his work on the prognosis of spasmophilia. — ZELLWEGER alleges that the majority of his spasmophilia convulsions occurred at a slightly earlier period; between the fourth and sixth months.

The results of our investigations in this respect can be seen in Diagram 2.

In our material spasmophilia is the most frequent cause of convulsions between the ages of 3 to 12 months; later the infection convulsions are predominant. To the second year belong 36.3 % of all the infection cases, which is about the same as the figure given by the authors previously mentioned.



### Delivery and Birth Weight

In his publication, which covers 365 cases, FAXEN is of the opinion that there are more pathological births in cases of epilepsy than in infection convulsions, i.e. 7 % and 3 % respectively, whereas in the group of infection convulsions there are considerably smaller children than in the epilepsy group. HERLITZ in his material on infection convulsions, comprising 744 cases, shows that there is no deviation from the normal birth weights. ZELL-WEGER's opinion is that the average birth weight of the patients affected with infection convulsions is somewhat less than of healthy children.

The percentage of prematurity in our material is 11.1. The prematurity birth rate of the district relative to normal deliveries during the period in question was, according to RÄIHÄ, 10—12 %. When we take into consideration the fact that mortality among the prematures is great before they attain the age of the children

Table 2.

## Birth Weight of Patients with Convulsions.

Birth Weight	Infection Convul- sions	Spasmo- philia	Miscella- neous Convul- sions	Uncertain Epilepsy	Total
Under 1 500 grams	—	1	2	—	3
1 510—2 000 "	2	2	1	—	5
2 010—2 500 "	9	4	2	—	15
2 510—3 000 "	13	10	8	2	33
3 010—3 500 "	23	16	18	4	61
3 510—4 000 "	31	19	15	7	72
4 010—4 500 "	8	3	1	1	13
over 4 500 "	2	1	2	—	5
—	—	—	—	—	207

in our material, we can estimate that in our material there are 1/3 more prematures than one would expect in normal material.

In the histories of our cases there were notes on the delivery in 205 cases, of which 191 were normal. The rest comprised 4 caesarean sections, 4 breech presentations and 6 deliveries with forceps. In no case did any severe asphyxia appear in the child at birth. — According to the birth records of the State Medical Board in Finland, about 4 % of the annual births are breech presentations and 3 % either caesarean sections or forceps deliveries, so that in this respect our material conforms to the normal. This confirms the conclusions drawn from earlier investigations that birth plays no essential part in the origin of infection and spasmophilia convulsions.

## Character of the Convulsions

The information on the earlier convulsions is based on the histories, the data of which were quite complete. For infection convulsions there was a previous history in 26.6 %; for spasmophilia patients the corresponding figure was 36.9 %.

On the other hand, information on the number of attacks and their duration is naturally less reliable, as it was often founded on

Table 3.

Number of Attacks in Infection and Spasmophilia Groups of Convulsions.

Number of Attacks	Infection Convulsions	Spasmophilia Convulsions
1	34	12
2—5	39	15
over 5	9	16
—	82	43

observations made by parents. Table 3 gives some idea of the number of attacks.

It might be mentioned that NORDENFELT observes that the number of attacks has no great influence on the later prognosis of the disease in spasmophilia.

In cases of infection convulsions ZELLWEGER considers the prognosis for epilepsy much better for patients with only one single attack than for those with repeated attacks.

Concerning the duration of the attacks we can only state that according to the histories they usually lasted 2—10 minutes. Moreover, it might be noted that the parents reported only 9 cases of infection convulsions in which the attacks lasted over 30 minutes.

According to ZELLWEGER the most usual period of attack during the day is in the afternoon or evening. In 57 cases in our material the time of the first attack was ascertainable from the history. Of these more than 1/2 (31) took place between 6 A.M. and 3 P.M.

#### Convulsions and Body Temperature

In the case of infection convulsions the temperature of the body was 39° in 66.7 % of the cases and over 40° in 20.7 %; whereas in spasmophilia 95 % were under 38°. — HERLITZ, who has specially studied the relation of fever to convulsions, states that the highest temperature in initial infection convulsions coincides with the attack. He gives a temperature over 39° for at least 75 %

Table 4.

Body Temperature in Infection and Spasmophilia Convulsions.

Body Temperature C°	Infection Convulsions	Spasmophilia Convulsions
36.0—36.9	1	33
37.0—37.9	5	24
38.0—38.9	23	3
39.0—39.9	40	—
40.0—40.9	15	—
over 40.9	3	—
—	87	60

of the cases and over 40° for about 25 %. ZELLWEGER's results on infection convulsions conform to these. The body temperature of  $\frac{1}{4}$  of ZELLWEGER's spasmophilia patients was above 38° during convulsions, which clearly conflicts with our own observations. Twenty % of FAXÉN's infection cases were without fever.

#### Appearance of Infection Convulsions

Infection convulsions have also been called initial convulsions, because the convulsions often appear as the first symptom of the disease. HERLITZ, whose material in this respect is the most extensive, has ascertained that in about 60 % of the cases the convulsions appeared within 24 hours of the first symptoms of the disease.

Table 5.

Appearance of Convulsions and First Symptoms of Disease.

Convulsions as first symptom.....	14	} 62 = 76.5 %
6 hours after first symptom .....	20	
24 hours after first symptom .....	28	
1—3 days after first symptom .....	14	} 19 = 23.5 %
3—7 days after first symptom .....	5	

Our small series also supports the opinion that when convulsions occur in infectious diseases, they are usually in the early stage of the disease.

### Diseases Giving Rise to Infection Convulsions

Infection convulsions can appear in most infectious diseases. The earlier literature mentions pneumonia, measles, scarlet fever, diphtheria, cystitis, etc. The literature on convulsions in connection with different infection diseases is very scanty. SAURIO ascertains that of 1000 whooping-cough patients in Finland 18 had convulsions as a secondary symptom, which gives an idea of the frequency of convulsions in connection with this kind of infectious disease in our country.

Table 6.

Infectious Diseases With Convulsions, According to Different Investigators.

Disease	Our Own Material	HERLITZ	FAXÉN	ZELL- WEGER
Infections of the Upper Respira- tory Tract .....	64	618	125	85
Pneumonia, Bronchopneumonia.	6	45	16	6
Infect. Dyspepsia .....	10	31	46	16
Vaccination Fever .....	1	7	—	2
Pyelitis .....	4	—	18	2
Erysipelas .....	—	33	2	1
Otitis Media .....	1	—	—	—
Urticaria, Sunstroke, Combustion etc. ....	—	—	—	5
Whooping-Cough, Measles, Ex- anthema Subitum, Epidemic Parotitis etc. ....	4	20	29	18
Unknown Infections .....	1	22	2	43
	91	776	238	178

In Table 6 we have combined the tables of FAXÉN, HERLITZ and ZELLWEGER with our own. All these series of cases are fairly uniform. In each series at least half of the infection convulsions can be attributed to inflammation of the respiratory tract.

### **Follow-Up Examinations .**

#### **Follow-Up Examinations and Mortality of Patients**

We have considered the prognosis the most important object of our investigation. We have paid attention chiefly to mental development, social adaptability, and the possible later appearance of convulsions.

During the period from Dec. 1, 1948 to May 31, 1949 we made written inquiries of all the patients included in our material or of their relatives. Of course it is difficult to obtain exact answers; conceptions as to normal mental development and social adaptability are very subjective and, in addition, patients and their parents may be inclined to give inaccurate information. We made out the questionnaire in a detailed but easily comprehensible form. To eliminate subjective opinions we included in the form inquiries about school attendance and grading, military service, trade, and in some cases marriage. We noted the occupation of the parents as well.

In cases where a renewed written inquiry failed to lead to a desired result, we resorted to a personal telephone call. We proceeded in the same way when the result of a written inquiry was not satisfactory. In the cases of those living out in the country, we had to make use of the assistance of the attendant health nurses. In the cases of patients who died after discharge from the hospital we received the necessary information from relatives or the church authorities. The military authorities gave us data on the health during service of conscripted men. For those treated later in other hospitals the hospital histories were used. The later development of 22 patients included in our material remained unclear. This means that in 90 % of the cases we succeeded in finding out the subsequent history of the children admitted to hospital for convulsions.

Of the 221 patients in our material 18 died in hospital, so that the mortality percentage was 8.1. The highest percentage figure was in the group of infection convulsions, or 11 %.

Since discharge from the hospital 25 patients have died, 16

of these within five years. In the case of the latter we have considered our period of observation too short for any reliable statement on their development. We have thus excluded these cases when drawing conclusions. These patients died from the following causes:

Bronchopneumonia	4	Diphtheria	1
Rickets	3	Gastroenteritis	1
Influenza	2	Meningitis	1
Pertussis	2	Unknown	1
Empyema pleurae	1		<hr/> 16

Nine patients died more than five years after their discharge from hospital. Four of them were killed in the war, 1 in a bombardment; the rest died of various diseases later. In addition 1 healthy patient went abroad. We have included these 10 cases in our follow-up examinations. The total mortality in our material is 19.5 %. The rates of mortality in the investigations of HJÄRNE and NORDENSON were 17 % and 15.4 %; these rates agree with ours when the cases of death due to war are excluded.

The essential material of our follow-up examinations thus comprises 155 living patients who have replied and the above-mentioned 10 who survived for a sufficiently long period of observation, or 165 cases in all. This represents 80.9 % of those who left the hospital alive. The period of follow-up examination varies from 7 to 29 years. In the group of infection convulsions it is on the average 15.6 years, in the spasmophilia group 15.7 years, in the group of miscellaneous convulsions 14.2 years and in the uncertain epilepsy group 14.4 years. In HERLITZ's work on initial convulsions the corresponding period was 7.8 years, in FAXÉN's material 3—12 years, in NORDENFELT's 6—18 years and in VOIGT's 5—16 years. All those examined by us should, under normal conditions, have attended elementary school one four-month term at least. Many investigators (BIRK, VOIGT, HALLMAN) make a particular point of the importance to be given to school attendance when the mental development and the social adaptability of a person are to be judged. In connection with the age question there is reason to note that in Finland, according to G. SUOMINEN, in over 80 % of the cases of epilepsy the disease starts before the age of 20.



It has been the purpose of our investigation to bring to light only distinct deviations from the normal, so that we have not considered intelligence tests necessary. Our final opinion of the actual condition of each patient has been based on a summary of all the information received by us.

Our results from follow-up examinations can be seen from Table 7.

Table 7.

Group	Treated in Hospital	Died in Hospital	Died Later		Alive, Informa- tion Obtained	Fate Un- known
			A	B		
Infection Convulsions. . . .	91	10	3	1	65	12
Spasmophilia Convulsions	61	4	8	3	43	3
Miscellaneous Convulsions	54	4	5	4	35	6
Uncertain Epilepsy. . . . .	15	—	—	2	12	1
Total	221	18	16	10	155	22

A: Too short a period of observation; information not taken into account in the conclusion.

B: Sufficiently long period of observation; information included in the conclusion.

### Results of the Follow-Up Examinations

The results of the examinations are best elucidated by Tables 8 and 9, showing the patients' susceptibility to renewed attacks of convulsions and their aptitude for schooling. The tables offer adequate points of departure for subsequent group analysis.

### Infection Convulsions

The follow-up examination in this group comprises 66 patients discharged from hospital. Of these 47 have developed normally in all respects. Moreover, they have had no convulsions since leaving the hospital.

In 10 cases the patients after discharge from the hospital have had convulsions at home, but not within the last six years.

Table 8.

Later Convulsions on Basis of Follow-Up Examinations.

Group	No. of Cases	No Convulsions at Present			Convulsions Continuously
		Mentally Healthy		Mentally Deficient	
		No Convulsions Since Discharge From Hospital	No Convulsions Since Early Childhood	No Convulsions Since Discharge From Hospital	
Infection Convulsions . . . . .	66	47	10	4	5
Spasmophilia Convulsions . . .	46	34	6	3	3
Miscellaneous Convulsions . . .	39	27	7	1	4
Total of Above	151	108	23	8	12
Uncertain Epilepsy . . . . .	14	6	3	1	4

Table 9.

School Attendance on Basis of Follow-Up Examinations.

Group	No.	University Students	Passed Lower Secondary School	Attended Lower Secondary School	Passed or Attended Elementary School	Incapable of Attending Elementary School Normally
Infection Convulsions . . . . .	66	4	10	15	32	5
Spasmophilia Convulsions . .	46	5	7	6	24	4
Miscellaneous Convulsions . .	39	2	4	6	21	6
Total of Above	151	11	21	27	77	15
Uncertain Epilepsy . . . . .	14	1	1	3	3	6

In these the convulsions appeared only in connection with pyrexia and stopped before the patients reached the age of 5 years. All 10 attend school at the moment or have been to school. Attendance at school or adaptation to a trade has not given any of them difficulty.

Four patients have had no attacks of convulsions since their discharge from hospital, but their mental development has been more or less retarded. One of these patients has not been able to attend school at all; another is at the moment in a school for backward children, where he finds difficulty in following the instruction. For 2 others school has been difficult and they have often failed to be promoted to a higher class. In no case has anything similar been ascertained in the families of these patients.

In the infection group there are still 5 patients who at times or continually up to the present time have had attacks of convulsions. One of these was later found to be a case of tetany. In another case it was found that similar convulsions had appeared in the family, leading even to death. Hereditarily there was nothing remarkable to observe about the remaining 3 patients. Two of them are in hospital for epilepsy; the third has so far been able with the aid of medicine to earn a living. In this last case it is possible that a brain injury at birth is responsible, as the patient then showed slight asphyxia.

In the whole group there are thus 6 cases which may be thought to have sequelae from the convulsions. Of these 3 are either in asylums as epileptics or otherwise in an undeveloped stage. In the case of 3 patients great changes have taken place in their personalities, but somehow they manage to earn their livelihood in the community.

The 6 cases mentioned comprise 9 % of all the infection patients examined. According to the investigation made in 1936 about 3 % of the whole population in Finland are mentally retarded. In the above classification of infection convulsions it became apparent that in addition to the 6 cases mentioned there were 3 who showed disturbances in mental development attributable to hereditary disposition or to difficult delivery at birth. We may consider these 3 cases to represent the amount of mental

disturbances in normal material. Thus it must be observed that the prognosis for children affected by infection convulsions may be worse as regards epilepsy and adaptability to society than in normal children. On the strength of our investigation about every tenth child affected with infection convulsions is in danger of acquiring sequelae of this nature. In drawing this important conclusion, one must take into account the small number in our series.

In Sweden HERLITZ is very cautious in expressing his opinion on the correlation between initial convulsions and genuine epilepsy. When speaking of patients affected with convulsions and of their later susceptibility to real epilepsy, he finds that percentage-wise this possibility is only small. The results of ZELLWEGER in Switzerland in respect of the prognosis are not so good as ours. Out of the 105 cases he examined, 15 were certainly or probably epileptics, pycnolepsy was diagnosed in 3 while 3 still had convulsions at times. Thus in  $1/5$  of the cases examined by him the convulsions had continued, but certainly in only  $1/3$  of these did epileptic changes in character or any more difficult mental disturbances appear.

Because of the smallness of our material it has been impossible for us to deduce which of the clinical symptoms point to a later bad prognosis. HERLITZ also refrains from expressing any opinion in this respect. On the other hand, ZELLWEGER observes that one single attack of convulsions very rarely gives cause for a bad prognosis. According to him, neither the intensity nor the length of the attack is of any great importance; instead he considers that the type of convulsion is important. In cases where the convulsions are unilateral, the prognosis is worse. In our material there was only one case of unilateral convulsions among the patients who were considered to have a bad prognosis. With the others the type was not clear or the convulsions were bilateral.

#### **Spasmophilia Convulsions**

In the spasmophilia group there were 61 patients. Of these the fate of 3 is unclear to us. Excluding the patients who died in hospital or at home, the examinations included 46 children. Of

these 34 have developed normally. They have all attended school fairly well, and the older ones, almost 1/3 of the number, are already earning their livings.

In 6 cases the patients have had attacks of convulsions at home but these did not continue after the children reached the age of 5 years. Attendance at school has not been difficult for them. Their mental development can be considered normal.

In the mental development of the remaining 6 cases there were considerable deviations from the normal. One of these patients developed quite normally at first, but since the war he has been continuously in an asylum. — Another patient was an imbecile under hospital care until his death 20 years later; in this case, however, there was strong hereditary tendency. — In another case it is probable that breech presentation at birth had a share in the unfavourable development. This patient died of the attacks within 10 years. There was nothing remarkable in the heredity of the remaining 3 patients. Their deliveries were also normal. These children have been treated in the hospital as cases of pure spasmophilia, nor has anything been found to point otherwise. The later development of all 3 has been remarkably slow. Only 1 of them, however, has had any attacks of convulsions.

Thus in the cases of 4 patients the cause may well have been spasmophilia. Two of them have had severe changes in personality, another 2 less severe, so that the latter 2 have been able to attend school. These cases represent 9 % of the patients examined in the group. In addition there were 2 cases in the group in which the cause of debility could have been an injury at birth or hereditary tendency. They would equal the debility figure in normal material. — Our result is thus the same as for the infection group: about 1/10 of the patients affected with spasmophilia convulsions may later show serious mental deficiencies.

In HJÄRNE's material of the same size there was not a single mentally deficient patient. In his material NORDENFELT arrives at the same result as we do. — VOIGT, the only investigator who at the same time examined comparative material, gives a much greater percentage figure. His material comprises 103 cases. His comparative material is of about the same size, comprising children

affected with rickets. In the former he has 45.6 % distinct cases of mental inferiority (*deutlich minderwertig*) and in his comparative material 22.3 %. On the basis of his investigation he considers it clear that convulsions are frequently followed by disturbances. We would join with NORDENFELT, who states: "The existence of a correlation between a previously passed spasmophilia and mental deficiency cannot altogether be excluded." Our material is small, but VOIGT's figures even then appear rather big. His work fails to show what proportion the cases examined was of all the cases of spasmophilia treated in the period considered.

#### Miscellaneous Convulsions

This group includes patients who probably belonged to the first or the second group, but as we wanted to keep those as definite as possible we put the cases about which we were not so certain into the miscellaneous group of convulsions. It must be noted that no patient even in this group has shown evidence of any organic disease of the brain or meningitis. In this group 39 patients were examined, of whom 27 have developed quite normally after discharge from the hospital.

In 7 of the remaining cases no attacks of convulsions have appeared since the age of 6 years and development has been normal since then.

In the group there are 5 patients that at the present moment are undergoing changes in personality. One of them has had no attacks since discharge from the hospital, but the child has not been capable of attending school and has been able to do simple farm work only under the supervision of others. — In the other 4 the convulsions have continued. They could not attend school nor can they perform the simplest kind of work.

In the whole group there are thus 5 cases showing distinct deviation from the normal. They form just less than 13 %; i.e. the same figure as in the preceding groups when we take into account that in normal material about 3 % are cases of mental deficiency.

### Uncertain Epilepsy

The cases in this group have been classified because the diagnosis made in hospital was considered uncertain. As stated in the beginning of this work, children over 3 years have been excluded, as the diagnosis of epilepsy made in them is more reliable. — The group is of course small, comprising in all 15 patients. The later progress of one of them remains unclear.

Six patients have developed normally. After discharge from hospital there have been no convulsions and they are attending or have attended school satisfactorily.

In 3 cases there have been no attacks of convulsions since early childhood. The later development of 2 of them has been normal, the third, however, attends a school for backward children.

In 1 case there have been no convulsions since discharge from hospital, but the patient is in need of constant treatment as incurably insane.

The remaining 4 cases have had convulsions continuously. Two of them died as the attacks became worse, at the ages of 10 and 18. The other 2 are still in an asylum.

Of the 14 cases in the group, 8 must be considered to have developed quite normally, so that the uncertainty of the early diagnosis is fully established. Moreover, 6 of these 8 patients have already passed the dangerous age of puberty. Although on the strength of the quality of the convulsions the cases in this group were suspected to be epilepsy, it must be observed that the prognosis even in these cases was not so bad.

### Summary

The authors have investigated the convulsions appearing in spasmophilia and infectious disease and especially their prognosis as revealed by follow-up examinations. The material comprises 221 children, treated for convulsions in the Helsinki Children's Clinic 1920—41. The cases were classified in four groups: infection convulsions (91 cases), spasmophilia (61), miscellaneous convulsions (54), and uncertain cases of epileptic convulsions (15).

In the follow-up examinations special attention was paid to the mental development, adaptability to society and continuance of the convulsions. The percentage examined was 80.9 and the period of observation 7—29 years. In the investigation it was observed that in the first three groups every tenth patient at the most underwent some mental changes.

### Résumé

Les auteurs ont fait des recherches sur les convulsions qui apparaissent dans la spasmophilie et les maladies infectieuses et spécialement sur leur pronostic révélé par des examens suivis. Le matériel comprend 221 enfants traités pour convulsions à la Clinique des Enfants d'Helsinki pendant les années 1920—41. Les cas ont été classés en quatre groupes: convulsions dans les infections (91 cas), spasmophilie (61), convulsions diverses (54) et cas incertains de convulsions épileptiques (15).

Lors des examens suivis, on a fait spécialement attention au développement mental, à la faculté d'adaptation sociale et à la persistance des convulsions. Le pourcentage des sujets ré-examinés a été de 80,9 et la période d'observation de 7—29 ans. On a observé au cours des recherches que dans les trois premiers groupes tout au plus un sujet sur dix subissait quelques changements mentaux.

### Zusammenfassung

Die Verfasser haben eine Nachuntersuchung an 221 Kindern, welche 1920—41 in der Kinderklinik in Helsingfors wegen Krampfen behandelt wurden, ausgeführt. Die Fälle werden in vier Gruppen geteilt: Infektions-Krämpfe (91 Fälle), Spasmophilie (61), Krämpfe verschiedener Art (54) und unsichere Fälle von Epilepsie (15). Besondere Aufmerksamkeit wurde der geistigen Entwicklung, der sozialen Anpassung und der Dauer der Krämpfe gewidmet. Ca 80 % der Fälle wurden 7—29 Jahre beobachtet. Höchstens 10 % der Fälle in den ersten drei Gruppen zeigten geistige Veränderung.



### Resumen

Los autores han hecho investigaciones sobre las convulsiones que aparecen en la espasmofilia y las enfermedades infecciosas y especialmente sobre su prognosis, revelada por dos exámenes seguidos. El material comprende 221 niños tratados por convulsiones en la clínica de niños de Helsinki durante los años 1920—41. Los casos han sido clasificados en cuatro grupos: convulsiones infecciosas (91 casos), espasmofilia (61), convulsiones diversas (54) y casos inciertos de convulsiones epilépticas (15).

En el momento de los exámenes seguidos, se ha consagrado una atención especial al desarrollo mental, a la facultad de adaptación social y a la persistencia de las convulsiones. El porcentaje de los sujetos examinados ha sido de 80,9 y el período de observación de 7 a 29 años. En el curso de las investigaciones se ha observado que en los tres primeros grupos como máximo un sujeto sobre diez sufría algunos cambios mentales.

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Received 6.4.1950.

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(FROM THE RADIUM CENTRE IN COPENHAGEN. CHIEF: JENS NIELSEN.)

## **Malignant Tumours in Childhood<sup>1</sup>**

by

**AAGE VIDEBÆK, M. D.**

Interest in childhood neoplasms may be traced far back in time, partly because they are of comparatively rare occurrence and partly because it is particularly tragic to find cancer in children.

In 1940 DARGEON, together with 11 other specialists, wrote a monograph on the subject in which they collected most of the cases reported in the literature. To this may be added several series which have been reported in the last decade: BLACKLOCK 100 cases from England, SCOTT 64 cases from New York, WILLIAMS 181 cases from England, ZUPPINGER 109 cases from Switzerland, and FLEMING & PEARCE 218 cases from Minnesota.

The figures representing the incidence of cancer in childhood, however, are derived from hospitals with widely different categories of patients. Even after the material has been increased by a large number of new series, the figures published cannot be said to convey a true impression of the absolute and relative incidence of malignant disease in childhood.

As early as 1908 the Danish workers FIBIGER & TRIER tried to evaluate the morbidity of cancer by counting all the cases under treatment on April 1. Among 1135 notified cases only 2 were children.

Since 1942 cases of malignancy in Denmark have been notified, voluntarily, it is true, to the Cancer Registry, where the death certificates are also inspected. In this way a fair knowledge

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<sup>1</sup> Aided by a grant from the Danish Anti-Cancer League.

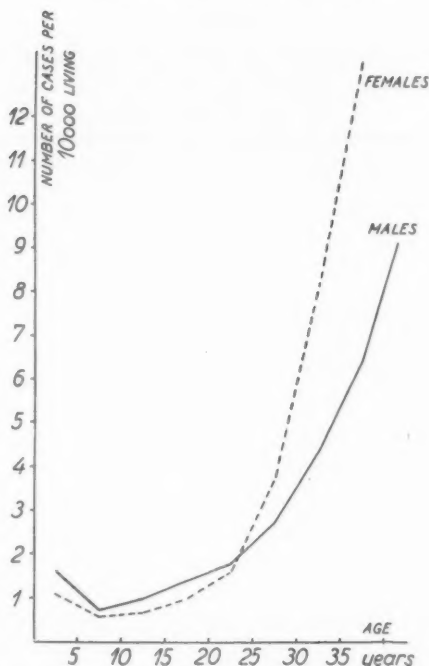


Fig. 1. Incidence of cancer in Denmark from 1942-1944 on the basis of figures from the Cancer Registry.

has been obtained of the incidence of cancer among the Danish population. The Registrar has kindly lent the writer the figures relating to the younger age groups from 1942-1944. These figures, plotted on Fig. 1, show that the incidence of cancer in childhood is far from approaching that of the more advanced ages. In the age group 0-10 years about 2 cases of malignancy have occurred per 10 000 living children, whereas the corresponding figure for e.g. the age group 70-74 years is about 130 per 10 000. The lowest incidence on the whole is to be found in childhood, *i.e.* about the seventh year of age, and it is not until after 20 years of age that a marked increase is apparent. In other words, malignant disease is comparatively rare in childhood.

Table 1

Deaths from cancer in Denmark during the period 1935—1944 in various age groups (in % of all deaths in the age group concerned).

Age Interval (years)	Males %	Females %
0—1 .....	0.1	0.1
1 .....	1.2	0.9
2 .....	2.9	3.0
3 .....	4.5	5.8
4 .....	4.6	5.1
5—9 .....	4.3	3.9
10—14 .....	3.0	5.1
15—19 .....	4.4	5.0
20—24 .....	3.9	3.3
25—34 .....	6.2	9.3
35—44 .....	11.2	23.6
45—54 .....	17.8	31.0
55—64 .....	22.2	27.2
65—74 .....	20.4	20.5
75—84 .....	13.6	12.7
85 and over .....	6.3	8.5

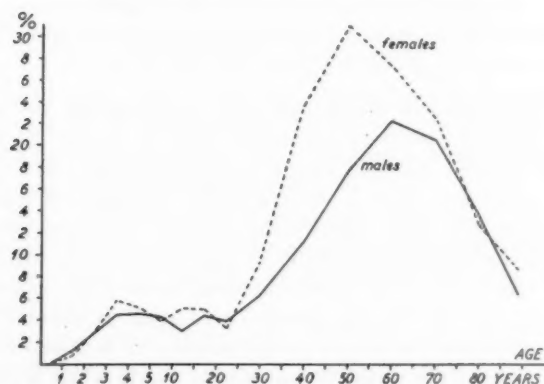


Fig. 2. Deaths from malignant tumours in various age groups in % of all deaths in the age group concerned (calculated on the basis of Causes of Death in the Kingdom of Denmark 1935—1944).

Table 2

Some deaths in Denmark (1937—1944) in  
the age groups 0—14 years.

Rheumatic Fever .....	101 cases
Diabetes Mellitus .....	107 »
Pulmonary Tuberculosis .....	415 »
Heart Disease .....	429 »
Measles .....	502 »
<i>Malignant Tumours</i> .....	<i>544 »</i>

Since, however, the chances of cure in childhood are still small compared with most other diseases, cancer in childhood is an important factor in the mortality statistics. It will probably be a cause of some surprise that, apart from the first year of life in which the deaths are due predominantly to diseases of the newborn, about every twentyfifth death in childhood is due to malignancy in the widest sense of the word (Table 1 and Fig. 2). Among females the mortality from cancer is highest around the age of 50, when approximately every third death is due to cancer; among males the summit occurs about 10 years later, at which age cancer is responsible for every fifth death. Despite the low incidence of cancer in childhood, the significance of malignant disease among children must not be neglected. This will be seen from Table 2, which shows that in Denmark malignant disease is a more common cause of death in childhood than e.g. diabetes mellitus, rheumatic fever, pulmonary tuberculosis, heart disease, and measles.

Childhood malignancy is nearly always of mesenchymal origin, whereas epithelial growths (carcinoma) occur but rarely. It will be seen from Fig. 3 that in the first two decades of life only about 20 % of the neoplasms are carcinoma, after 35 years of age at least 80 %, and after the seventieth year of age more than 95 %.

Any organ and any tissue in the child appears to be able to form the origin of a neoplasm. In children, as in adults, malignant growths may arise in any region, and since childhood growths arise mainly from interstitial tissue, their localization is even less consistent than in adults, whose new growths are so often epithelial

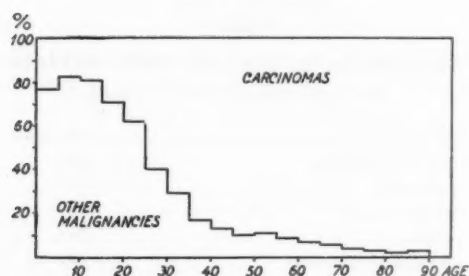


Fig. 3. Epithelial and mesenchymal neoplasms in various age groups in % of total cancer in the age group concerned.

and therefore commonly encountered in certain organs or certain systems. A topographic classification of new growths in childhood is, therefore, difficult. Moreover, the tumours are in several cases of a more or less embryonic character, being derived from more than one germ layer, which further complicates the histologic classification.

According to the Danish Cancer Registry 276 cases of malignant disease among children under 15 years of age were notified during the period 1942–1944. The distribution is listed in Table 3. One-third of the cases were systemic diseases, primarily leukaemia of the acute type. Deducting this group, the neoplastic

Table 3

Cases of malignant tumours in children under 15 years of age notified to the Danish Cancer Registry during the period 1942–1944.

Hodgkin's Disease + Leukæmia + Myeloma .....	84	patients = 30 %
Sarcoma .....	56	" = 20 "
Brain Tumour .....	54	" = 20 "
Skin Carcinoma .....	11	" = 4 "
Renal Tumour .....	11	" = 4 "
Cancer of the Digestive Tract .....	5	" = 2 "
Abdominal Cancer .....	4	" = 1 "
Cancer of the Male Genitalia .....	4	" = 1 "
Cancer of the Female Genitalia .....	2	" = 1 "
Other Sites .....	45	" = 16 "
		276 patients

nature of which has been the subject of much discussion, there is another large group designated as sarcoma. Owing to the rather small numbers involved, the Cancer Registry did not like to give further details about the sub-grouping of the growths. Therefore, too much importance must not be attributed to the figures in Table 3. A number of the growths classified as brain tumours were histologically benign but clinically malignant. Bone sarcoma, subcutaneous sarcoma, and tumours of embryonic character make up part of the cases designated as sarcoma and tumours of other sites.

It is beyond doubt that childhood tumours constitute a separate chapter within oncology. It is striking that the lowest incidence of cancer for males as well as females occurs during pre-puberty. The lowest point on the curve showing the incidence in Fig. 1 is presumably interpretable as the point of intersection between the declining curve representing the growths peculiar to childhood and the rising curve representing typical but early cases of growths common in adult and elderly individuals. The actual childhood tumours are sarcomas or mixed tumours the pathogenesis of which is entirely different from that of tumours in adults. In certain cases, hereditary factors have been thought to influence the development of certain new growths and particularly their early manifestation (JACOBSEN). Children suffering from cancer may possess a more marked inherited predisposition to develop cancer than healthy children (SCHNORREBUSCH & KUJATH, VIDEBÆK), but a more comprehensive study of this problem is required. The hormonal level of children is low and rather indiffernt, and this may be the reason why the incidence of various kinds of neoplasms is rather low and fairly alike in boys and girls. Many types of tumours occurring in adults appear to be influenced by the hormonal level, and a sex proportion deviating considerably from 1 is not uncommon. In some instances it is reasonable to interpret childhood tumours as dysontogenetic, embryonic growths, but otherwise the genesis of tumours peculiar to childhood appears to be as obscure as that of cancer on the whole.

*Acknowledgement.* My thanks are due to Dr. Johs. Clemmesen, Registrar of the Danish Cancer Registry, for providing some of the figures quoted.

### Summary

The incidence of malignant disease in childhood is about 1-2 cases per 10 000 children. About 4 % of all deaths among children over 1 year of age are due to malignant tumours.

The lowest incidence of cancer for both sexes is in prepuberty, about the seventh year of age.

Actual childhood tumours occur before this age and are predominantly sarcoma and mixed tumours which are interpreted as a separate group of a special pathogenesis thought to be independent of the hormonal level.

The few carcinomas which occur in childhood are chiefly epitheliomas, whereas carcinoma of the alimentary tract is even more uncommon.

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### AAGE VIDEBÆK: *Les tumeurs malignes de l'enfance.*

L'incidence de la malignité pendant l'enfance est d'environ 1-2 cas pour 10 000 enfants. Environ 4 % des causes de mort chez les enfants au dessous de 1 an sont dues aux tumeurs malignes.

La plus basse incidence du cancer dans les 2 sexes est à la prépuberté, sept ans environ.

Les tumeurs réelles de l'enfance se présentent avant cet âge; ce sont surtout des sarcomes et des tumeurs mixtes qu'on interprète comme un groupe séparé par pathogénie spéciale que l'on pense être indépendante du niveau hormonal.

Les quelques carcinomes qui se présentent pendant l'enfance sont principalement des épithéliomas tandis que le carcinome du tractus digestif est plus rare.

### AAGE VIDEBÆK: *Die malignen Tumoren im Kindesalter.*

Die Häufigkeit der Malignität im Kindesalter ist etwa 1-2 Fälle pro 10 000. Ungefähr 4 % aller Todesfälle bei Kindern über 1 Jahr sind verursacht durch bösartige Tumoren.

Das niedrigste Vorkommen von Malignität bei beiden Geschlechtern ist vor der Pubertät, um das 7. Lebensjahr.

Echte Tumoren kommen vor diesem Alter vor und sind vorwiegend Sarkome, sowie Mischgeschwülste, die aufgefasst werden als eine spezielle Gruppe mit besonderer Pathogenese, von denen man annimmt, dass sie unabhängig vom Hormonspiegel sind.

Die wenigen Carcinome, die in der Kindheit vorkommen, sind hauptsächlich Epitheliome. Carcinome des Verdauungstraktes sind besonders selten.



AAGE VIDEBÆK: *Los tumores malignas en la infancia.*

La frecuencia de enfermedades malignas en la infancia es de 1 a 2 casos en 10 000 niños. Cerca del 4 % de muertes entre niños de mas de un año son debidos a tumores malignos.

La menor frecuencia del cancer en ambos sexos ocurre durante la época antes de la pubertad, alrededor del septimo año.

Los tumores actuales de la infancia se presentan antes de ésta edad, siendo la mayoría sarcomas y tumores mixtos que se interpretan como un grupo separado de patogenía especial independiente del nivel hormonal.

De las pocas carcinomas que ocurren en la niños, la mayor parte son epitelomas, sin embargo la carcinoma del aparato digestivo es menos común.

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Received 22.6. 1950.

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## **Antihyaluronidase Content of Serum in Children Suffering from Hemolytic Streptococcal Infections, Rheumatic Fever and Other Diseases**

by

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Human serum contains antibodies against hyaluronidases of different origin. Results of several investigations published in the last few years show that the antihyaluronidase content is higher in children with rheumatic fever than in children suffering from other diseases. The antihyaluronidase mentioned in these articles neutralises the hyaluronidase from hemolytic streptococci. There are different views as to the diagnostic value to be attached to the determination of the antihyaluronidase content in rheumatic fever.

In this investigation the antihyaluronidase content of serum was determined by the mucin-clot-prevention test. The method described by QUINN was used.

This method is based on the fact that a clot is formed by acidifying a solution of hyaluronic acid containing protein. No clot is formed if the hyaluronic acid has been hydrolysed by hyaluronidase. In this investigation a filtrate of a culture of hemolytic streptococci in serum broth was used as hyaluronidase. A dilution of 1:2048 of this filtrate still hydrolyses 1 cc of a 0.04 % solution of potassium hyalurate. The hyaluronidase content of this fluid remains constant for months, if kept at a low temperature.

The chief of the laboratory of the pediatric clinic, Dr. M. M. P. PAULSEN, prepared the potassium salt of hyaluronic acid from umbilical cords. One part of a 0.15 % solution of this salt in distilled water was mixed with an equal part of 10 % diluted horse serum and two parts of distilled water. This mixture must be recently prepared and can be kept a couple of days only. The determination was made in the following way. Ten serum dilutions are made (1:16, 1:32, etc.). To each tube containing

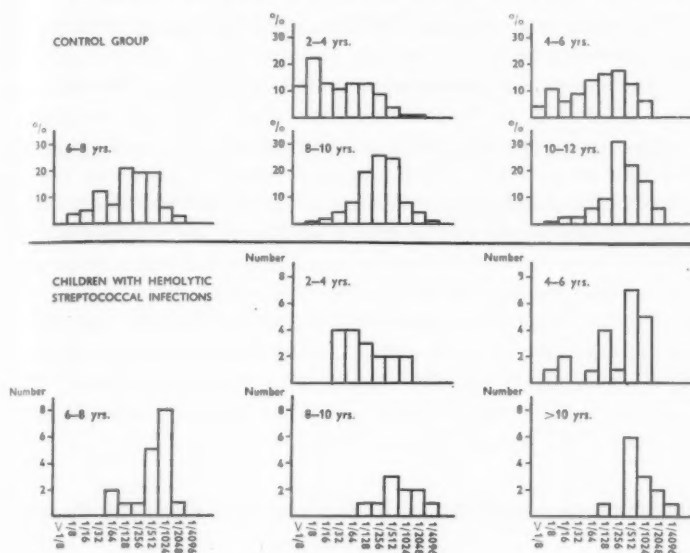


Fig. 1.

1 cc of diluted serum, 0.5 cc of the diluted hyaluronidase solution is added. This hyaluronidase dilution must be 16 times more concentrated than the highest dilution which still hydrolyses the hyaluronic acid present in 1 cc of the above mentioned mixture. The tubes are kept at room temperature for 15 minutes. Next they are put in an ice bath and 1 cc of the mixture of potassium hyalurate and horse serum is added to each tube. The tubes are incubated at 37° C for 20 minutes. After they have been placed in an ice bath and 0.2 cc of a 2 N solution of acetic acid has been added the reaction can be read. A clot is present in those tubes which contain sufficient antihyaluronidase to neutralise the hyaluronidase. One serum of which the antihyaluronidase content is known serves as control.

### 1. Antihyaluronidase Titers in Healthy Children and in Patients Not Suffering From Hemolytic Streptococcal Infection

The results were arranged according to the children's ages. In the age group of 2-4 years 252 sera were examined, in the group of 4-6 years 133 sera, in the group of 6-8 years 117 sera,

in the group of 8—10 years 106 sera and in the group of 10 years and older (up to the age of 14) 97 sera.

The average antihyaluronidase titer increased as the children grew older (Fig. 1). Proportionally more sera with low antihyaluronidase content were found in the youngest age group than in the older ones. The antihyaluronidase content of the serum varied greatly in each age group. We must stress the fact that the division of the children into two groups according to the presence or absence of infection with hemolytic streptococci was rather arbitrary. Mild inflammations of the upper respiratory tract caused by hemolytic streptococci occur frequently in children and often remain unobserved. It is quite possible that some of the children in the first group actually should be in the second group. The increase in the average antihyaluronidase titer with age has been mentioned by QUINN and by FRIOU.

## **2. Antihyaluronidase Titers in Children With Hemolytic Streptococcal Infections**

The results in this group could not be expressed in terms of percentages because the number of cases was too small. In the successive age groups given the numbers of the sera examined were 17, 23, 19, 10 and 13 respectively. In the figures the number of cases is plotted. The numbers being too small no conclusion can be drawn. One had the impression, however, that the titers were generally higher than those in the children of the first group. This is corroborated in the literature by more material (FRIOU and HARRIS and HARRIS).

In 23 children suffering from scarlet fever the antihyaluronidase content was determined twice. The first blood sample was taken from the third to the sixth day after the patient fell ill. The second determination was made a fortnight later. In 9 patients no increase was noted and in 5 patients the titer had fallen. FRIOU has mentioned that the highest antihyaluronidase titer is reached two weeks after the beginning of the disease. The patients whose sera were examined in this investigation were treated with penicillin. KILBOURNE and LOGE, MINKENHOF, PEETERS

and VISSER found that the production of antistreptolysin is counteracted by the administration of penicillin. The same may be true for the production of antihyaluronidase.

### 3. Antihyaluronidase Titers in Children With Rheumatic Fever

In 11 children the antihyaluronidase content of serum was determined in the acute phase of the disease (Table I).

Table I

No.	Sex	Age	Titer	No.	Sex	Age	Titer
1	Female	11 yrs	1: 512	7	Female	7 yrs	1: 8192
2	Female	9 "	1: 1024	8	Male	7 "	1: 4096
3	Male	8 "	1: 2048	9	Male	13 "	1: 4096
4	Female	4 "	1: 1024	10	Female	9 "	1: 1024
5	Female	9 "	1: 2048	11	Female	8 "	1: 8192
6	Male	6 "	1: 8192				

Thus high antihyaluronidase titers were found in all these cases except 1. In only 3 cases were the titers above the highest values found in the first two groups. The determination of the antihyaluronidase content cannot provide us with evidence in the diagnostics of rheumatic fever, as far as our judgement can be based on this little material. But a high antihyaluronidase titer can confirm the diagnosis. The number of cases of rheumatic fever in children is not large enough in Amsterdam to permit the collection of sufficient material.

QUINN and HARRIS and HARRIS found, that the average antihyaluronidase content is higher in children with rheumatic fever than in children not suffering from this disease. This is confirmed by HARRIS and NAGLE. The latter investigators never observed higher titers than 1:800 in children with hemolytic streptococcal infections. Titers of 1:1024 or more were found only in children with rheumatic fever, viz. in 45 % of the children. It is the opinion of these investigators that the occurrence of antihyaluronidase titers of 1:1024 and higher has a great diagnostic

value in rheumatic fever. But such a great difference between the titers in the three groups was not found in this investigation. In only 3 patients with rheumatic fever was the antihyaluronidase content of the serum higher than the highest titer found in the other two groups. One patient suffering from rheumatoid arthritis also had an antihyaluronidase titer of 1:8192. The results in this child will be mentioned later on together with those of other children suffering from the same disease.

The other children whose sera were examined had at the time of the first bleeding no signs of rheumatic fever. They had, however, previously had one or more attacks; some children had valvular lesions.

Table II

No.	Sex	Age	Titer
1	Female	9 yrs	1: 1024
2	Female	10 "	1: 64
3	Male	10 "	1: 1024
4	Female	7 "	1: 128
5	Female	5 "	1: 1024
6	Female	3 "	1: 512
7	Female	12 "	1: 1024
8	Male	12 "	1: 512
9	Female	10 "	1: 512

Table III

No.	Sex	Age	Titer
10	Male	12 yrs	1: 64
11	Female	7 "	1: 8192
12	Male	7 "	1: 256
13	Male	9 "	1: 16
14	Male	10 "	1: 256
15	Male	13 "	1: 16
16	Male	6 "	1: 512

Nine of these 16 children (see Table II) had not received chemoprophylaxis till the time when the first blood sample was taken. The other 7 children (see Table III) had been treated regularly for several months with sulfadiazine in a dosage of 0.25 g twice daily. The antihyaluronidase titers were lower in the children who had recovered than in those who were acutely ill.

Generally, lower antihyaluronidase titers were found in the children who received chemoprophylaxis. In 1 patient, however, the antihyaluronidase titer remained high for a long period in spite of chemoprophylaxis. In this group definite conclusions cannot be drawn either because of the limited number of cases.

But the two latter facts are made probable by the results given in the next table (Table IV). In several patients the antihyaluronidase content of the serum was determined repeatedly.

It appears from this table that the antihyaluronidase titer falls during recovery and rises again when a relapse occurs. In patient No. 8 a temporary rise in the titer was observed after discharge from the hospital, while no clinical signs were present.

The antihyaluronidase titer generally fell still further during chemoprophylaxis.

The administration of sulfadiazine is interrupted during the summer. In 5 of the 7 children no rise in the antihyaluronidase titer was seen during that period. In patient No. 19 the antihyaluronidase content of the serum did rise and in patient No. 20 the rise in the titer was accompanied by general symptoms (apathy, loss of weight).

Four out of 5 children suffering from rheumatoid arthritis had a low antihyaluronidase content of the serum. In a 13 year old girl the antihyaluronidase titer was 1:8192. During the administration of adrenal corticotrophic hormone (cortrophine "Organon") the titer fell to 1:256. Hemolytic streptococci were cultured from the throat. Three weeks later the antihyaluronidase titer rose to 1:1024 in spite of continuous treatment. These results cannot be explained, because the factors which stimulate and counteract the production of antihyaluronidase are still unknown.

### Comment

The average antihyaluronidase content of serum increases as the children grow older. The antihyaluronidase content varies greatly within each age group of children not suffering from hemolytic streptococcal infections. One got the impression that the antihyaluronidase content is generally higher in children with hemolytic streptococcal infections. The following reservation must be made: first: the number of patients suffering from hemolytic streptococcal infections is too small to warrant definite conclusions; secondly: the division into the first two groups is rather arbitrary because inflammation of the upper respiratory tract caused by hemolytic streptococci often has a latent course.

Table IV

No.	Sex	Age	Date of Examination	Clinical Data	Therapy	Titer
1	Female	11 yrs	10.12.49	Ill 3 weeks; E.S.R. 50	Acid. acetylo-salicylic.	1: 512
			5.1.50	E.S.R. 20; no complaints	Acid. acetylo-salicylic.	1: 64
2	Female	9 yrs	5.4.49	Ill a fortnight; E. S.R. high	Amidopyrin	1: 1024
			27.4	No change	"	1: 1024
			10.5	Exacerbation	"	1: 2048
			22.6	Amelioration	"	1: 1024
			22.9	E.S.R. normal		1: 512
			2.10	No complaints		1: 128
			5.1.50	" "		1: 32
3	Female	9 yrs	10.11.49	Ill 1 week; E.S.R. high	Acid. acetylo-salicyl.	1: 2048
			1.12	E.S.R. 21	"	1: 512
			5.1.50	E.S.R. normal		1: 128
4	Male	6 yrs	4.3.49	Ill a couple of days	Acid. acetylo-salicyl.	1: 1024
			15.3	Exacerbation		1: 8192
			17.3	No change	Amidopyrin	1: 8192
			31.3	Slight amelioration	"	1: 4096
			15.4	Afebrile	"	1: 2048
			27.4	Temp. slightly elevated	"	1: 2048
			10.5	Temp. elevated; E. S.R. elevated	"	1: 8192
			23.6	Temp. and E.S.R. normal	"	1: 2048
			6.7	No signs		1: 2048
			22.7	" "		1: 1024
5	Female	7 yrs	1.4.49	Rheumatic fever in 1948		1: 4096
			1.7	No complaints		1: 2048
			15.11	Recurrence	Amidopyrin	1: 8192
			30.11	No change	"	1: 8192
			10.12	No change	"	1: 8192
			5.1.50	E.S.R. normal	"	1: 512



Table IV (Cont.).

No.	Sex	Age	Date of Examination	Clinical Data	Therapy	Titer
6	Female	7 yrs	17.2.49	Rheumatic fever in '47; no complaints		1: 128
			13.3	Shoulder pain; E. S.R. normal		1: 512
			12.4	E.S.R. elevated	Acid. acetylo-salicyl.	1: 1024
			27.4	No signs	"	1: 256
			12.5	" "	"	1: 256
			2.6	" "		1: 256
			6.7	" "		1: 256
			15.9	No signs		1: 128
			21.9	Pain in left ankle; E.S.R. elevated	Acid. acetylo-salic.	1: 256
			5.1	No symptoms		1: 128
7	Female	10 yrs	10.3.49	No signs		1: 64
			17.3	Pain in left leg; E. S.R. elevated	Acid. acetylo-salicyl.	1: 256
			12.5	No signs	"	1: 256
			16.11	" "		1: 128
8	Male	7 yrs	22.3.49	'48 Rheumatic fever; still high E. S.R.	Acid. acetylo-salicyl.	1: 4096
			15.4	No change	"	1: 2048
			27.4	E.S.R. falls	Amidopyrin	1: 512
			10.5	" "	"	1: 512
			27.5	Fever; E.S.R. more elevated	"	1: 4096
			23.6	E.S.R. falls	"	1: 2048
			22.7	E.S.R. normal		1: 256
			23.9	3 weeks after discharge; no signs	sulfadiazine	1: 4096
			29.10	No signs	"	1: 512
			27.11	" "	"	1: 256
9	Female	4 yrs	5.1.49	Rheumatic fever for 3 weeks	Penicillin	1: 1024
			17.2	E.S.R. falls		1: 256
			31.3	" "		1: 128

Table IV (Cont.).

No.	Sex	Age	Date of Examination	Clinical Data	Therapy	Titer
9			15.4	E.S.R. normal		1: 64
			10.5	No complaints		1: 128
			5.10	Chemoprophylaxis started	Sulfadiazine	1: 128
			21.12		"	1: 64
10	Female	9 yrs	1.7.49	Ill 5 days	Acid. acetylo-salicyl.	1: 1024
			20.9	E.S.R. normal		1: 128
			30.11	Chemoprophylaxis 7 weeks	Sulfadiazine	1: 128
11	Male	6 yrs	22.3.49	Rheumatic fever in 1945 and 1947; 8 weeks chemoprophylaxis	Sulfadiazine	1: 512
			10.5	No sulfadiazine for 1 month (leucopenie)		1: 2048
			10.6	Again chemoprophylaxis	Sulfadiazine	1: 256
			23.6		"	1: 128
			1.7		"	1: 128
			29.7	Pain in left arm	Acid. acetylo-salicyl.	1: 512
			15.9	No complaints		1: 256
			30.10	Chemoprophylaxis	Sulfadiazine	1: 64
			25.11		"	1: 32
12	Female	9 yrs	10.3.49	Rheumatic fever in '48		1: 1024
			15.4	4 weeks chemoprophylaxis	Sulfadiazine	1: 256
			10.5		"	1: 1024
			1.7		"	1: 512
			16.9	No sulfadiazine during summer		1: 512
			30.11	Sulfadiazine 2 months	Sulfadiazine	1: 256

Table IV (Cont.).

No.	Sex	Age	Date of Examination	Clinical Data	Therapy	Titer
13	Male	12 yrs	17.3.49	1 year of chemoprophylaxis	Sulfadiazine	1: 64
			10.5	No sulfadiazine for 6 weeks (leucopenie)		1: 2048
			16.9	No sulfadiazine		1: 4096
14	Female	5 yrs	24.2.49	Rheumatic fever in '48	Sulfadiazine	1: 1024
			2.6	2 months' chemoprophylaxis		1: 1024
			25.9	No sulfadiazine during summer months		1: 512
			1.12	Chemoprophylaxis	Sulfadiazine	1: 128
15	Female	10 yrs	6.2.49	Recovered from chorea	Sulfadiazine	1: 512
			20.5	No complaints		1: 512
			25.11	Sulfadiazine 2 months		1: 256
16	Male	13 yrs	12.5.49	In '47 rheumatic fever; no complaints	Sulfadiazine	1: 512
			23.6	Chemoprophylaxis 1 month		1: 128
17	Male	7 yrs	10.3.49	Chemoprophylaxis 6 months	Sulfadiazine	1: 256
			4.11		"	1: 128
			4.12		"	1: 64
18	Male	9 yrs	1.7.49	Chemoprophylaxis 2 years	Sulfadiazine	1: 256
			16.9	No sulfadiazine during summer months		1: 256
			1.12	Sulfadiazine 2 months	Sulfadiazine	1: 64
			19.12		"	1: 32

Table IV (Cont.).

No.	Sex	Age	Date of Examination	Clinical Data	Therapy	Titer
19	Male	13 yrs	12.5.49	Chemoprophylaxis 2 months	Sulfadiazine	1: 16
			23.9	During summer no sulfadiazine		1: 512
			30.11	Chemoprophylaxis 2 months	Sulfadiazine	1: 32
20	Female	7 yrs	17.3.49	18 months' chemoprophylaxis	Sulfadiazine	1: 8192
			10.6		" "	1: 2048
			1.7		"	1: 2048
			28.9	No sulfadiazine during summer		1: 4096
			30.11	2 months' sulfadiazine	Sulfadiazine	1: 1024
21	Male	10 yrs	22.3.49	Rheumatic fever in 1948		1: 1024
			30.4	Chemoprophylaxis 3 weeks	Sulfadiazine	1: 512
			16.9	No sulfadiazine in summer		1: 256
			2.11	Sulfadiazine for 7 weeks	Sulfadiazine	1: 128
			2.12		"	1: 128

While investigating sera of children suffering from rheumatic fever we noted:

1. that the antihyaluronidase titer was generally high in the acute phase of the disease. In only 3 cases, however, were the antihyaluronidase titers above the highest value found in the other groups;
2. that the titer rises and falls in accordance with the disease;
3. that the antihyaluronidase content of serum diminishes gradually during the administration of small doses of sulfadiazine. This fall in the antihyaluronidase content could perhaps be

explained by the fact that chemoprophylaxis may prevent infection with hemolytic streptococci. Also in this part of the investigation the limited number of patients does not warrant definite conclusions.

It is our opinion that the determination of the antihyaluronidase content of serum can be of diagnostic value in rheumatic fever, but cannot provide us with diagnostic proof.

### Summary

The serum antihyaluronidase content in 705 children was determined. The mean titer increases with age.

The serum antihyaluronidase content in children suffering from rheumatic fever was compared with that in children suffering from hemolytic streptococcal infections and with the titers in children of the control group. The titer was generally high in children with rheumatic fever in the acute phase of the disease. A decrease in the titer was observed when the patients recovered and a further decrease was mostly seen during the period of chemoprophylaxis.

Three only out of the 11 patients who were in the acute phase of the disease had antihyaluronidase titers which were above the highest values found in the other groups.

No definite conclusions can be drawn owing to the small number of cases of rheumatic fever. The impression was gained, however, that the determination of the serum antihyaluronidase content may be of diagnostic value in rheumatic fever, but will not provide us with the diagnostic proof.

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MARIE R. H. STOPPELMAN: *Le taux d'antihyaluronidase dans le sérum chez des enfants atteints d'infections streptococques, de fièvre rhumatismale et d'autres maladies.*

On a déterminé le taux d'antihyaluronidase dans le sérum chez 705 enfants. Le titre moyen augmente avec l'âge.

Le taux d'antihyaluronidase dans le sérum chez des enfants atteints de fièvre rhumatismale a été comparé avec celui d'enfants atteints d'infections à streptocoques hémolytiques et avec celui d'un groupe de contrôle. Le taux était généralement élevé dans la fièvre rhumatismale à la phase aiguë de la maladie. Une diminution du taux était observé quand les malades allaient mieux; une nouvelle diminution était principalement vue pendant la période de chimioprophylaxie.

3 seulement des 11 malades qui étaient dans une phase aiguë de la maladie avaient un taux d'antihyaluronidase au-dessus de la plus haute valeur trouvée dans les autres groupes. On ne peut tirer aucunes conclusions définitives du fait du petit nombre de cas de fièvre rhumatismale. Cependant il semble que la détermination du taux d'antihyaluronidase dans le sérum peut avoir une certaine valeur pour le diagnostic de fièvre rhumatismale, mais ne nous fournira pas le diagnostic lui-même.

MARIE R. H. STOPPELMAN: *Der Serum-Antihyaluronidasegehalt bei Kindern mit Streptococc-Infektionen, rheumatischem Fieber und anderen Krankheiten.*

Es wurde der Serum-Antihyaluronidasegehalt bei 705 Kindern bestimmt. Der durchschnittliche Titer steigt mit dem Alter an.

Der Serum-Antihyaluronidasegehalt von Kindern, die an rheumatischem Fieber litten wurde verglichen mit solchen, die Infektionen mit haemolytischen Streptococcen hatten und mit einer Kontrollgruppe. Der Titer war im allgemeinen hoch bei Kindern mit rheumatischer Infektion während der akuten Phase. Ein Abfall des Titers wurde beobachtet mit der Gesundung der Kinder und eine weitere Abnahme war meist vorhanden während der Zeit der Chemoprophylaxe.

Nur 3 von 11 Patienten, die in der akuten Phase waren, hatten Antihyaluronidasetiter, die höher waren als die höchsten, in anderen Gruppen gefundenen Werte.

Es können keine endgültigen Schlüsse gezogen werden wegen der geringen Zahl der Fälle mit rheumatischer Infektion. Es wurde jedoch der Eindruck gewonnen, dass die Bestimmung des Serum-Antihyaluronidasegehalts diagnostischen Wert bei rheumatischen Infektionen haben kann, ohne einen diagnostischen Beweis liefern zu können.

MARIE R. H. STOPPELMAN: *La cantidad de antihialuronidasa en el suero de niños atacados por infecciones estreptococas, de fiebre reumática y otras enfermedades.*

Se ha determinado la cantidad de antihialuronidasa en el suero de 705 niños. La concentración media aumenta con la edad.

La cantidad de antihialuronidasa en el suero de niños atacados por fiebre reumática se ha comparado con la de los niños atacados por infecciones estreptococas hemolíticas y con la de niños testigos. La concentración era generalmente elevada durante la etapa aguda de la fiebre reumática. Se observó un descenso de la concentración durante la recuperación, y una mayor disminución durante el período de quimioprofilaxia.

Solamente 3 de los 11 enfermos demostraron durante la etapa aguda de la enfermedad concentraciones de antihialuronidasa superiores a los valores más altos encontrados en los otros grupos.

No se puede deducir ninguna conclusión definitiva de tan pocos casos de fiebre reumática. Sin embargo se adquiere la impresión de que la determinación del contenido de antihialuronidasa en el suero puede ayudar al diagnóstico de la fiebre reumática, pero sin ofrecer ninguna verdadera prueba.

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Received 28.6. 1950.

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## **The Undergraduate Teaching of Pediatrics**

by

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The considerably increased importance of pediatrics in the general scheme of public health should induce a reconsideration of the position of this subject in the medical curriculum. Earlier, and indeed even today in some quarters, pediatrics forms part of the subject of internal medicine, and the teaching is supervised by the Head of that department. This must be regarded as a very unsatisfactory arrangement. Pediatrics deals with human beings who are continuously changing, owing to development and growth. The pediatrician has problems of his own, different from those of other specialities. In my country, this was realized earlier than anywhere else. Already 105 years ago, pediatrics was separated from internal medicine and became a special subject with its own instruction and examination. The extent and importance of the subject, not only from the point of view of the prevention of disease, but also for the promotion of optimal physical power and a happy emotional balance, have made, or should have made, pediatrics one of the principal branches of medical teaching.

Since children in need of a physician, can never, in all instances, have access to specialists, but have to be treated by general practitioners, the teaching and training in pediatrics must be adapted to the actual requirements. This is, unfortunately, not the rule. In order to encourage knowledge about the care of children, and the treatment of the diseases of childhood, — something absolutely necessary for the competent young doctor of today — the teaching of pediatrics must be intensified and rationalized. The extent of the pediatric studies cannot be fixed by any universally applicable rules, as there are, of necessity, many

Read at the Sixth International Congress of Pediatrics. Zürich. July 24th 1950.



factors of importance, varying from one country to another. Such factors are the standard of public health, facilities available for treating the sick child, economic factors and the enlightenment of the population from a medical point of view. Only a few general, universally applicable, principles can be put forward.

The ever-increasing range of the medical curriculum makes it essential to limit, carefully, the various branches. However great is the desire to improve the teaching in a branch that has grown more important there is no other choice than either to increase the time of the total length of the medical studies or to cut down the time devoted to subjects that have become less important. The former will meet with the difficulties of economy and organization, and the latter with the resistance of the representatives of the subjects selected as victims. For these reasons, a compromise has to be arrived at between what is theoretically desirable and possible in practice. This makes it the more important to define clearly the object of present-day teaching in pediatrics. Its aim must be to supply such fundamentals in the care of children and treatment of children's diseases as are indispensable to the ordinary general practitioner.

What are these fundamentals? They must include the somatic and mental development and growth of the normal child at different periods of its life, together with significant physiological data, breast- and artificial feeding of infants, the composition of the food necessary for the different periods of growth, diseases resulting from a deficient diet, general principles of the physical and mental health of children, the neonatal period and its disorders, the premature child, disturbances in growth, digestive irregularities, including diarrhea, intestinal worms, intussusception, catarrhal infections of the respiratory passages and the complications they may lead to; specific, acute and chronic, infectious diseases common in children; acute meningitis and encephalitis; allergic diseases; congenital and acquired cardiac lesions; the more common blood diseases and types of hemorrhagic diathesis; convulsions, including spasmophilia; encephalopathy and oligophrenia with mongolism; hypothyroidism and diabetes; Bright's disease, orthostatic albuminuria and urinary tract infections; common

functional disturbances (e.g., anorexia, enuresis and encopresis, disturbed sleep, common behaviour problems); eczema, neurodermitis, seborrhoic and contact dermatitis, pemphigus, impetigo and pyoderma, scabies; head and body lice; ordinary and conspicuous, operable or otherwise treatable, malformations; national legislation for the care of, and the public health institutions for, children; general and specific prophylaxis; demographic problems of natality and infantile mortality; theoretical and practical aspects of a program for the promotion of child health; general principles of therapy and the determination of the dose of drugs in childhood. This list of conditions covered by the pediatric studies can, broadly speaking, be said to apply to the greater part of Europe. It can, of course, be modified, according to the diseases that are particularly frequent in the various countries, especially the usual infectious diseases (e.g., malaria, leishmaniasis, rickettsial diseases, etc.) or prevalent diseases originating in popular customs, the national resources and the cultural and general hygienic standards.

An optimal program for the instruction and training in pediatrics has to be rather extensive. It demands a careful organization of the plan of study, and great efficiency in the execution of it, if it is not to encroach too much on the total amount of time set apart for the medical curriculum. Various methods and principles have been tried but I feel much inclined to doubt that any academic teacher in pediatrics could be fully satisfied with the results he has reaped from his personal efforts. The efficiency of pediatric teaching can be ascertained and judged only from the optimal result of the studies, e.g., from the thoroughness of the knowledge and experience, imparted and imbibed, as they manifest themselves at examinations. At the present stage of progress it should be possible to agree on some fundamental and generally applicable principles.

An essential point is that the teaching of pediatrics, or at least the most important, the practical part, should be deferred until towards the end of the medical studies. Though in itself one of the principal subjects, pediatrics, comprising as it does all kinds of important diseases in children, is connected with virtually

every clinical subject. It has much in common with all other branches and is partly based on them. Before taking up pediatrics, the student should have acquired a broad view of medical science as a whole. His study of other clinical subjects should have opened his eyes to the patient as a fellow-creature and to the effects of disease on the patient himself, as well as on those about him, i.e., the psychosomatic and social-medical factors. He should be animated by a wish to learn the art of prevention, which is largely a pediatric task.

Another thing to be desired — something which is, no doubt, also generally accepted — is that the teaching of pediatrics should not take the form only of theoretical lectures delivered simultaneously to a large number of students, in connection, perhaps, with demonstrations of cases. The emphasis must be placed on an individual practical guidance in the course of work in wards and outpatient departments. The student will, then, be in a position to contribute actively to his own training, by observation at the bedside. The usefulness of practical instruction at the bed of a patient has long been realized. As early as 1842, the Council of Teachers of Karolinska Institutet at Stockholm made the following statement: "A knowledge of children's diseases can never be satisfactorily acquired from books, or communicated in lectures *ex cathedra*. What is wanted is studies at the sick-bed, to a far larger extent than in the case of the diseases of adults."

This, in turn, presupposes a third condition, viz., that the number of students, during the practical part of the teaching, has been strictly limited. Otherwise, it will be virtually impossible to allow individual attention to a sufficiently large number of cases. The practical training can be performed in connection with more theoretical clinical studies. It can take place after the final examination, during a so-called practical year (internship), or perhaps the two types of teaching should, preferably, be combined.

However the practical training be organized it has to be supervised by experienced assistant hospital doctors (instructors). They should be interested in teaching and able to inspire the students with a feeling of personal responsibility for the patients assigned to them.

During his practical work the student can by no means hope to obtain personal experience of even the majority of diseases affecting children, in all their innumerable varieties. A minute study and a critical estimation of a number of common illnesses constitute a more useful preparation for the duties of a general practitioner than a large number of superficial impressions at many types of diseases, some of which may be extremely rare. To know where information can be obtained is often a better way than to cram the memory with too many facts.

The length of time sufficient for acquiring a proper knowledge of pediatrics depends largely on the methods of teaching, whether the student is simultaneously occupied with other subjects, and whether the pediatric course is limited to a certain period or runs through several terms. Some parts of the pediatric course can be started before clinical pediatric training in the proper sense of the word, has commenced. For example, somatic and mental development and growth can be studied in advance at the beginning of the clinical studies. Physiological data can be gathered in connection with the preclinical physiological teaching. Prenatal care and the importance to the fetus of the general condition of the mother, as well as the neonatal period and its disorders, are matters that can be dealt with in the course of the obstetric studies, etc. The student has then time to digest the knowledge thus acquired before the start of his practical training in pediatrics. If the pediatric teaching is concentrated to one single period, exclusively occupying the attention of the student, it should be desirable that the time devoted to the theoretical and practical training should be at least 3—4 months or, better 5 months. A period shorter than this will hardly enable a student to gain personal experience of the mental and somatic development of the normal child and the most common diseases, such as a general practitioner must know.

The number of hours, weeks or months is, however, less significant, from the point of view of the teaching, than the personal quality of the student himself and the efficiency of the methods adopted for the teaching.

Unless the receptivity, intellectual ability and capacity for

work of the student come up to the mark, he will be unable to turn the theoretical instruction to good account or to benefit from his practical studies. For this reason, a selection has to be made from students who feel inclined to study medicine. This selection has to be careful and restricted to those who have reached a proper standard of maturity. Only then can there be any guarantee of satisfactory results, provided of course that the teaching methods are good enough. The position of the future doctor in the social life of the community should not be forgotten and he therefore should be an educated person who knows how to behave with a proper measure of tact, consideration and tolerance. With regard to the premedical studies, particular stress should be laid on a general good humanistic education, on foreign languages and on chemistry, physics, and biology. Unfortunately, knowledge of foreign languages is often scanty, and it should, perhaps, not be out of place, at an International Congress like this, to emphasize the desirability of taking steps to improve matters in this respect.

Formerly, particular importance used to be attributed to organized lectures, as a teaching method, with or without simultaneous demonstrations of illustrative cases. Nowadays, this form of teaching is in many places regarded as antiquated and by some as superfluous, as it is considered that the knowledge imparted to the students could just as well have been read from text-books. To abolish lectures altogether would probably, be going too far. Particularly as far as the main features of development and growth, and of physiological variations during that process, are concerned a systematic presentation of facts in the form of lectures may well be justified from a pedagogic point of view. It should, however, be accompanied by tables, diagrams, figures etc. A student will best remember what he has done or experienced personally. He will also remember a large part of what has been demonstrated to him and only a small part of what he has heard and listened to. From the teaching point of view, lecturing without simultaneous demonstrations of tables, pictures, X-ray films, lantern slides, motion pictures, disease cases or autopsy material is less effective than when combined with an explanatory accompaniment of that sort. In these circumstances there appears

to be an obvious justification for including lectures, though only as one of the methods adopted for the teaching of pediatrics. A lecture offers a good teacher many opportunities, among other things to present his subject in an individual light and to help the student to apply the knowledge he has obtained from other sources. A lecturer will also be able to place his subject in a wider perspective, particularly by drawing attention to its social-medical and psychosomatic significance. Moreover, a lecture will serve the purpose of supplementing such parts of the text-books as may have become out of date, and of introducing new conceptions. By quoting special articles from the medical papers, and monographs, a lecturer is in a position to encourage the more advanced students to pursue their studies beyond the stipulated demands of the course.

With regard particularly to the acquisition of knowledge of diseases, other forms of collective teaching are, however, undoubtedly more useful, as these induce those attending to take a more active part. I am referring to what we call *clinical conferences* or *seminars*. On these occasions, a discussion of a typical case of a disease is opened by a student and afterwards debated from a pathological, clinical, therapeutic, psychosomatic and social point of view etc., by students, doctors and other specialists with practical experience in the care of the sick child, such as social workers, psychologists, play-therapy assistants, dietitians and public health nurses. In the course of these proceedings both students and others are being led into interchanges of opinion that will open up new aspects, such as no ordinary lecture would do. The aim of this particular form of teaching is to place the sick child in the foreground and to shed light on the significance of environment in the origination of a disease, as well as on the reactions of the disease on the sick child and its nearest relatives. A student who, before such a clinical conference, has read the text-book's account of the disease in question will afterwards, without the slightest doubt, have acquired a fresher and more lasting recollection of it and of its significance to the child and its surroundings. Cases typical of every common disease or group of diseases may suitably be discussed at such clinical conferences,

one by one. These conferences also produce a strong impression of the correlation between pediatrics and other clinical and theoretical branches of medicine, especially internal medicine, surgery, biochemistry and physiology. In so far as representatives of these special branches can be persuaded to take part, the conferences will gain still more in value and importance by their contributions to the debates.

Another form of collective instruction where an active participation of the audience forms an essential feature, is *diagnostic conferences* or, as they are also called, *clinical pathological conferences*. In this instance, a summary is given of the history, clinical findings and course of a disease, in a case not previously known to the audience, a case that has ended in death and autopsy. Copies of this summary are distributed, a few days or a week ahead of the conference, to participating doctors and students. The diagnosis and disease symptoms of the case are then discussed. The leader of the conference is the only one who has been previously informed of the postmortem findings and it is up to him successively to throw light on the arguments propounded in the course of the debate, by weighing their strength, either mildly criticizing or accepting the suggestions, according to circumstances. When the discussion has been concluded, the leader of the conference will sum up the various proposed diagnoses and, then, disclose the pathological findings. The students who are naturally anxious to compete between themselves, and with the hospital doctors, in arriving as closely as possible to the correct diagnosis are, consequently, tempted into active participation in the debate.

Similar discussions should also be arranged after a death of a clinical case before a postmortem has been performed, with the students, as a matter of course, participating. Autopsy should be obligatory when a child has died at a teaching hospital, since, apart from a visual repetition in anatomy and topography at different ages, it will offer the student an opportunity of checking the clinical diagnosis and of correctly estimating disease symptoms, clinical findings and laboratory reports.

Selected autopsy cases that demonstrate important clinical



facts, or where the findings in themselves offer problems, should now and then be collected and discussed at *pathological conferences*. After a short presentation and repetition of the clinical data submitted by a clinician, a pathologist will demonstrate the pathological and histological findings, adding a short résumé of the case from his point of view. This may be followed by a discussion.

The *individual instruction* that can be given to the student, in connection with his duties in a ward or outpatient department (clerkship), will be of special benefit to him, in his practical training. This is an absolutely indispensable part of a proper scheme of teaching. Here the student will come into contact with the patients. He will gain practice in recording adequate case histories and in making primary observations, in discussing a tentative diagnosis, based on the disease history and the findings, and in suggesting suitable therapy, all this under the supervision of some senior colleague attached to the same department. It is important for the student to see the sick child in the outpatient department or immediately after admission to hospital, since a clinical picture may completely change within a few hours. For this reason, a system with resident students should be preferable.

A good result of this part of the teaching depends, apart from the available case material, on the following two factors: 1. The group of students, simultaneously attached to one department, should be as small as possible. 2. The resident physician should be interested and experienced in the technique of medical instruction and guidance. The student must not function only as some kind of handy-man to him. The latter should rather appear as a friend and senior colleague, anxious to help the student in his training. The student should be imbued with a feeling of carrying out responsible work, with the same duties and authority as devolve upon a young, inexperienced doctor.

The *ward rounds* should prove useful, provided that the student takes an active part. The number of participants should be limited enough to allow the student to get close to the bed-side and to have his share in the discussion. The case should be demonstrated by the student in charge while the teacher should intervene in the discussion only with a view to correcting, elucidating or



supplementing his description, and guide him as he gives his reasons for a diagnosis. The teacher should also try to place the particular case in a broader perspective and to encourage all those present to take part in the discussion. The case should be examined in all its aspects. Psychosomatic, social and prophylactic points of view should also be considered. A good teacher will prove his ability by detecting interesting points even in banal cases and encouraging those present to contribute their views.

In the course of his practical work at the department, the student should, circumstances permitting, personally attend to, at least one typical case from each group of diseases (e.g., cardiac diseases, convulsions, diarrhea). In order to check this, the resident physician might, at the initiation of the work, give each student a list of all these different groups of diseases. Here, he could subsequently make a mark for each case assigned to a student. The student should be present at, or himself perform, such minor medical operations as occur in the ward or outpatient department (e.g., lumbar puncture, pleural tap, and pneumothorax treatment) and technical procedures (e.g., blood transfusion, intravenous drip), as well as train himself in the various cutaneous tests. By working in a children's welfare centre he will have ample opportunities to investigate and study healthy children at various stages of development. Work in a department for infants and pre-matures will give him experience of the care and treatment of sick and feeble children.

More favourable results might be expected from the teaching, were the students to be less crammed with facts and allowed better chances to discover things for themselves and to reflect on what they have learnt and observed. The student should be taught to use text-books and periodicals, and, on occasions, be referred to original works that may satisfy his curiosity and, as far as the more gifted students are concerned, spur them on to research of their own. They must now and then enjoy some definite, and regular, leisure from systematic teaching, in order to enable them to relax and refresh their mind, and to pursue studies of their own. They need time to think over what they have learnt, to allow new-acquired knowledge to strike root and to adapt old knowledge to new.

*Examination* should go on, in a disguised form, during the whole period of ward work and, over and above that, an examination with practical tests should conclude the pediatric course. This is necessary, in order to enable the teacher to form an opinion of the effect of his own teaching, and to trace any blanks in the knowledge acquired by the students that may call for an intensification of the instruction in these particular respects. Whether the examination takes place in writing or orally, or whether it is performed only once, at the end of the course, or several times during its progress, may be of minor importance, the essential point being that it should be combined with practical tests designed to reveal the capacity of the student to judge concrete cases of healthy or sick children as a doctor.

A doctor in training should learn, not only for an examination but for life. Pediatrics is in a state of considerable progress. It is probably one of the branches of medicine where the advance has been, and is, most rapid. In order not to lag behind in these great forward strides, the young doctor must continue to learn. There is much justification for the saying that a doctor will never be in a position to have nothing more to learn; he has, in fact, to go on learning for the whole active part of his life. It is, therefore, indispensable for him to be taught, even during his pre-clinical and clinical studies, the technique of keeping abreast with progress so as not to deprive himself of the benefits of important discoveries. He should be encouraged to study the latest medical periodicals. The advantages of doing so will, perhaps, be most obvious at the clinical conferences where the most recent opinions and experiences should be presented.

The medical profession must not become a commercial occupation, either wholly or in part. It has to remain a calling based on science. By collecting, and turning to good account, the personal experiences from his daily work, and by satisfying his wish for more professional information, and of keeping up to date by reading current medical reviews and newly published text-books, a competent doctor will improve the knowledge he retains from his academic studies. He then gains the great satisfaction of performing his humanitarian tasks with an ever-growing ability and

insight. He should participate in medical conferences, congresses and hospital staff meetings, and perhaps especially take part again and again, at some years' intervals, in refresher courses. In these, new methods for examination and treatment, invaluable to the practitioner, should be taught and then it will be possible to keep up with the progress and to come into contact and profit from fruitful discussions with colleagues.

Finally, a few words about *specialization* in the study of pediatrics. This implies a knowledge and experience that go far beyond the limits of those of a general practitioner. Such a competence can be gained only by prolonged work as an assistant doctor in a pediatric clinic, or outpatient department, where the standard is high, there is a great variety of patients and where the management, and scientific achievements are satisfactory. Only this can guarantee a fully satisfactory specialized teaching. As a rule, university clinics are best for training specialists. On account of the long time necessarily required for the pediatric studies, and the limited number of permanent members on the medical staffs of the university clinics who can be detached for this task, and, further, because of the great demand for pediatricians, pediatric hospitals other than the university clinics must also be used.

In order to secure a uniform and high level of training, there must be some controlling organisation, and it should be the duty of this organisation to authorize the use of such pediatric hospitals for teaching. This controlling organisation can either take the shape of a Special Committee of the National Medical Association or be appointed by the government. When deciding the conditions on which the training of pediatric specialists can most suitably be entrusted to a pediatric hospital, particular regard has to be paid to the personality of the chief physician of the hospital, to the size of the staff, the number of beds, the type of variety of patients, which should not be too uniform, the number of autopsies, the scientific activities, access to library, frequency and standard of the scientific conferences held at the hospital, the possibilities of maintaining contacts with other branches of medicine and, perhaps most important of all, the will to provide the necessary means for a specialist training.

As to the time required for these studies, less than 3 years would hardly suffice for assimilating and digesting all the knowledge that a specialist must command. The optimal time is, probably, 5 years. As a matter of course, this time must not be shared with other branches of study, but given exclusively to pediatrics. The teaching must not be too uniform, scientific or require too much laboratory work, but be mainly clinical and practical. The doctor must not allow himself to be so intensely absorbed in research into some special problem that he fails to pay attention to other parts of the pediatric art of healing. The purpose is to train pediatric practitioners, not scientists or laboratory workers. On the other hand, the future pediatrician must necessarily have scientific interests. He should preferably perform minor scientific tasks by himself and take an active part in scientific gatherings, with demonstrations and lectures. The activities must not restrict themselves to clinical routine work only, where no more is done, and no other interest satisfied, than the bare requisites of what is absolutely wanted in order not to neglect any case. The clinical work must rather be kept on a level commensurable with that of a university clinic, and the specialist in being must devote himself wholeheartedly to the perfection of his training, by taking every opportunity to learn what the whole hospital offers, as well as through a careful study of pediatric literature.

In his work, he should be guided by the experience of the senior doctor of the outpatient department or ward, and, in his turn, having become a teacher himself, assume personal supervision and responsibility for a new arrival, to take his former place. The necessary years of study should, preferably, be apportioned to different pediatric hospitals, as the type of patient may vary and the specialities may often be somewhat different from one children's hospital to another. In this way, the experience gained will be more varied than if the entire period of study were to be spent at one hospital. Visits to foreign clinics are exceedingly useful as a finish to training, an observation that has, perhaps, been best realized by the pediatricians of small countries.

In the pediatric specialist teaching a particular emphasis must be laid on an understanding of the psychosomatic aspect of pedi-

rics and the psychology and psychiatry of children, since the majority of cases in this field are of functional disorders. There are few departments of medicine where the health and behaviour of an individual are so intimately allied to those of another as in the relationship of mother and child. Much attention should, for this reason, be paid to the proper teaching of this part of pediatrics by the medical staff. The specialist training should also include work for a time at a child guidance clinic. Similarly, the social-medical side of pediatrics should be carefully observed. Every pediatric specialist should have collected personal impressions of the significance of social conditions in the origination, course and prevention of disease. He should have been active in the various branches of social-medical pediatrics, e.g., child welfare centres, day nurseries, children's homes, school medical services, visits to homes of the children, etc. The pediatrician must continually bear in mind the important place of prophylaxis. In this instance, the demand for an up-to-date knowledge about diagnosis, treatment and prevention of the specific infectious diseases is evident. Should knowledge of these diseases not be sufficiently to the front, on account of lack of variety of cases at the hospital where the specialist training had taken place, a supplementary course should be taken, combined with work at a hospital for epidemic diseases.

Provided that the specialist training at the approved hospitals be of good repute, no special examination should be called for. On the other hand, it is fairly natural that such an examination is regarded as a necessary guarantee in big countries, like the United States of America, with their numerous approved training hospitals. Should an examination be considered to be indispensable, it should, of course, be demanded from all training hospitals, not only from those outside the university clinics.

If it be important that the young pediatrician should have acquired a satisfactory knowledge of all the various parts of his branch of study, no less importance should be attached to his keeping up his standard by continued studies, by paying attention to the pediatric reviews, by participation in gatherings of scientific specialists, staff meetings, supplementary medical courses, etc. The specialist is, no doubt, more inclined to bear these points in

mind than the general practitioner who is often pressed for time.

I have already said, that whatever his resources, no professor in pediatrics is at present at all likely to be satisfied with his teaching. We are still groping for a really satisfactory way of imparting a practical pediatric instruction. We are also, all of us, regrettably wanting in pedagogic knowledge. We do what we can, by intuition, by the lessons we once learnt from our own teachers, and from progressive colleagues. An adequate technique and use of all the modern resources for pediatric teaching have become of considerable practical importance, much more so than earlier. It is up to us who teach pediatrics to do our utmost to improve the results of our teaching, in order to make it equal to the demands we are asked to meet.

### Summary

The increasing importance of child health makes a revision of pediatrics in the medical curriculum necessary. Pediatrics should be made one of the main clinical subjects and the teaching of pediatrics should be effective enough to guarantee satisfactory practical knowledge of the healthy and sick child. The importance of selection of the teachers and the students, restriction of the number of accepted students, organization of the teaching program and better technique of the teaching is stressed. The individual bedside training in the wards or at the out-patient department should be more emphasized. The collective teaching in the classroom should only be a minor part of the program and be improved by the introduction of new methods aiming at a more active participation of the audience. The length of the pediatric curriculum should preferably be not less than 3 months, the optimal time probably being 5 months including clerkship or internship. The course should be postponed until the end of the clinical undergraduate studies and terminated by an examination.

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#### A. WALLGREN: *L'enseignement de la pédiatrie.*

L'importance croissante de la santé infantile rend nécessaire une révision de l'enseignement pédiatrique au cours des études médicales.

La pédiatrie devrait être considérée comme un des sujets essentiels de la clinique et son enseignement devrait être suffisamment efficient pour assurer des connaissances pratiques satisfaisantes en matière de santé et de maladie chez l'enfant. L'importance du choix des professeurs et des étudiants, la limitation du nombre de ces derniers, la mise en point

du programme et l'amélioration des méthodes d'enseignement sont soulignées. L'information individuelle au lit du malade et en polyclinique devrait être poussée d'avantage. L'enseignement collectif en salle de cours ne devrait constituer qu'une part moins importante du programme et devrait subir des réformes dans le sens d'une participation plus active de l'auditoire.

La durée de ce stage ne devrait pas être inférieure à 3 mois, la durée optima étant probablement de 5 mois, assistantat ou internat compris. Le stage devrait être remis à la fin des études cliniques et se terminer par un examen.

A. WALLGREN: *Der Unterricht in der Kinderheilkunde.*

Die wachsende Bedeutung der Gesunderhaltung des Kindes macht eine Revision der Ausbildung in der Kinderheilkunde notwendig. Die Pädiatrie soll eine der hauptsächlichen klinischen Fächer sein und die Ausbildung in der Kinderheilkunde soll wirksam genug sein um zu garantieren, dass genügend praktische Kenntnisse über das gesunde und kranke Kind vorhanden sind. Die Bedeutung der Auswahl von Lehrern und Studenten, die Beschränkung der Zahl der angenommenen Studenten, die Organisation des Studienplans und eine verbesserte Technik des Unterrichts wird angestrebt. Der persönliche Unterricht auf den Krankenabteilungen am Krankenbett oder in der Ambulanz soll stärker beachtet werden. Der gemeinsame Unterricht im Hörsaal soll nur ein kleiner Teil des Lehrplans sein und soll verbessert werden durch die Einführung neuer Methoden mit dem Zweck eine stärkere aktive Teilnahme der Hörschaft. Es ist ratsam, dass die Länge der Ausbildung in Kinderkrankheiten soll nicht weniger betragen als drei Monate. Die günstigste Zeitdauer wäre 5 Monate einschliesslich Praktikantenzeit. Dieser Kurs soll am Schluss der klinischen Studienzeit angeschlossen und durch ein Examen abgeschlossen werden.

A. WALLGREN: *La enseñanza de pediatría a los estudiantes.*

La creciente importancia de la salud infantil obliga a una revisión de la pediatría en los cursos de estudios de medicina. La pediatría debería llegar a ser uno de los temas clínicos principales y su enseñanza lo suficientemente efectiva para garantizar un conocimiento práctico satisfactorio de los niños sanos y enfermos. Se subraya la importancia de la selección de los profesores y de los estudiantes, limitación del número de estudiantes aceptados, organización del programa de estudios y mejor técnica de la enseñanza. La preparación individual a la cabecera del paciente en los hospitales o en el servicio de consulta debería estar más considerada. La enseñanza colectiva en las aulas debería ocupar solamente una parte mínima del programa y mejorarse con la introducción

de nuevos métodos a fin de obtener una participación más activa del auditorio. La duración de los cursos de pediatría preferiblemente no debería ser inferior a 3 meses; probablemente lo mejor sería 5 meses incluyendo el tiempo de secretaría y prácticas. El curso debería ser postergado hasta el fin de los estudios clínicos de graduación y terminarse por un examen.

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Received 14.10 1950.

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## CASE REPORTS

### Exchange Transfusion as Treatment in Poisoning

by

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Poisoning from accidental ingestion of medicaments intended for external use and other preparations is a condition constantly confronting the pediatrician. As most of these poisons act rapidly and as the parents are often unable to give any information about the quantity or the nature of the poison ingested, prompt and adequate treatment often presents considerable difficulties. But even the treatment of poisoning from known substances or preparations is not always an easy matter either. During the last few years I had the opportunity of observing two such cases of severe poisoning in which exchange transfusion produced such striking results that they were thought to merit report.

*Case 1.* A 4 year old girl was admitted in the spring of 1946 to the Flensburg Children's Hospital, Malmö. The mother had telephoned to the hospital and reported that her child, whom she had seen 15 minutes before without noticing anything unusual, now sat subdued and pale on the floor. Around her were a number of chloramine-T tablets. On examination at the hospital 20 minutes later the child was in very poor condition and lay completely flaccid and unconscious with an imperceptible radial pulse. No reflexes could be elicited. The skin, particularly of the legs and the feet, was cold and clammy. The heart beat was regular with a frequency of 90—100 per minute. Respiration was shallow but not rapid. She was stimulated with metrazol and after about five minutes the pulse could again be felt. The blood pressure was 135/100 mm. Further doses of metrazol were administered. Gastric lavage was attempted but soon had to be interrupted owing to shock. Gastric lavage produced half a tablet that had fastened in the mouth of the catheter. When brought into contact with hydrochloric acid the tablet gave off chlorine. The child then showed a slight improvement but her condition gradually deteriorated and her skin turned pinkish and afterwards dark red with a tinge of blue. About 200 ml fresh whole blood was infused intramedullary into the tibia and as this transfusion seemed to produce a beneficial effect, exchange transfusion was decided upon. Phlebotomy, in which a vein at the bend of the elbow was chosen, was performed without anesthesia and without any apparent reaction on the part of

the child. About 500 ml of the blood was abstracted at the same time as a similar quantity of fresh whole blood was infused. In the course of the transfusion the patient's skin assumed a more normal appearance and the blood withdrawn became lighter in colour. The child now began to offer resistance and finally had to be restrained. On the way from the operating theatre to the ward the child suddenly sat up on the wheeled stretcher, recognized and called to her mother, who happened to be standing in the hall. The child's condition improved rapidly, but she was still very drowsy and not herself again until after about five days. Laboratory tests made during the course of the illness showed no evidence of icterus or albuminuria, nor did the urinary sediment show anything remarkable.

*Case 2.* A 2 year old girl was admitted in 1949 to the Children's Department of the Central Hospital, Kristianstad. In this case, which was also dramatic, the child had happened to get hold of a bottle of marking ink, i. e. a mixture of nigrosine, which is very poisonous, aniline dye, aniline oil and benzene. The child had poured the contents of the bottle into a glass and pretending it was juice had drunk it up. The person in charge of the girl did not think it would harm the child much but soon noticed that she became apathetic and wanted to lie down on the floor. On return of the mother one and one half hours later the girl was driven to the hospital without delay. On admittance the child was in very poor condition. She was flaccid and stuporous, but remarkably enough, she was rather clear mentally. The mouth and the hands were stained with the ink, but in addition hereto the entire face had turned an ugly bluish black. Even the very small vessels were observable through the skin, as if the child had been given an injection of some dye intravascularly. Moreover, on the slightest exertion she became obviously cyanotic and the entire body turned a bluish black colour. There were obvious associated movements of the nostrils in connection with respiration, which was otherwise not forced or increased, but rather shallow and irregular. The pulse was thready and accelerated and intermittently irregular. In view of the poor condition of the patient, and as 90 minutes had elapsed since the ingestion of the ink, gastric lavage was not attempted. When I tried to examine her, she cried, lost consciousness, and became ash-grey and flaccid; the pulse was now thready and so rapid that it could not be counted, and the child began to gasp for breath. Her condition was now threatening. She was stimulated with nikethamide and Sympatol (Ingelheim) but her skin was still cold and clammy and she still appeared to be in very bad condition. She was immediately carried up to the ward and placed in a warm bed with hot-water bottles. Further medication with stimulants produced a slight improvement, but her skin remained cold and clammy and the bluish-black cyanotic discolouration persisted as did the respiration symptoms. In view of the obviously critical con-

dition of the patient exchange transfusion was decided upon. Blood was infused into the right cubital vein and allowed to flow from an incision made in the left radial artery. At first no blood flowed from the artery owing to the general collapse of the vascular system, nor did it commence to flow until a few hundred milliliters of blood had been infused and heparin administered. The blood abstracted first was dark brown to lilac but gradually became lighter in the course of the transfusion. Also the colour of the face became much lighter, and the general appearance of the patient gradually improved. Altogether 1100 ml of blood were abstracted and 1200 ml infused. There was continuous improvement in the condition of the patient during the first few hours after the transfusion, but during these there were also a few attacks of fairly threatening apnea with cardiac insufficiency which were successfully treated with stimulants and inhalation of oxygen and carbon dioxide. About six hours after the transfusion the child sat up of her own accord in bed and appeared to be brighter. She felt thirsty, took her mug herself, and drank unaided. The colour of her skin was now practically normal, respiration was still rapid but regular and the pulse was also normal. The following morning — about another six—seven hours later — she sat up in bed and played and looked as healthy and bright as if nothing had happened. Neither could any evidence of icterus, hematuria or albuminuria be demonstrated but only a few granular casts in the urinary sediment.

In both cases, then, there was serious poisoning which would apparently have ended fatally had recourse not been had to special therapy. In both instances the beneficial effect of blood transfusion was so striking that it must be considered to have saved the lives of these infants. Theoretically, it sounds only logical to remove from the body as much of the ingested poison as possible. Transfusion will admittedly have no direct effect on the poison absorbed by the various organs, but as the concentration of the poison in the blood decreases, the poison will presumably be able to diffuse also out of the organs, in which the concentration will likewise fall. This ought also to decrease the risk of organic damage.

The question then arises as to when blood transfusion is indicated. The method should of course be used only as a last resort in very serious cases, particularly in those cases in which the poison causes blood changes, e.g. methemoglobinemia, etc. The method is therefore indicated for treatment of poisoning from aniline preparations, the large group of aniline dyes, as well as medical preparations such as antipyrine, antifebrin, acetanilid, phenacetin, etc., and poisonous substances of another type, viz., potassium chlorate, chloramine and carbon monoxide.

In some of the manuals dealing with these questions the method in question is recommended, i.e. ample transfusion, if necessary with venesection. Nevertheless in the toxicological literature few reports of such

treatment are available. Blood transfusion has admittedly been employed, and in some instances also venesection, but very seldom a thorough exchange transfusion. As the mortality rate among such cases of poisoning is very high it was thought justified to draw attention to the extreme value of exchange transfusion in the treatment of poisoning, particularly as it is fairly easy to perform, and, if carried out with due care, practically free of risks.

### Summary

A description is given of 1 case of chloramine poisoning and 1 case of aniline poisoning, both in children whose lives were apparently saved by treatment with exchange transfusion.

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STEN AXTRUP: *Deux cas d'empoisonnement traités par exsanguino-transfusion.*

On rapporte un cas d'empoisonnement par la chloramine et un cas par l'aniline, l'un et l'autre chez des enfants ramenés apparemment à la vie par une exsanguino-transfusion.

STEN AXTRUP: *Vergiftungsfälle behandelt mit Austausch-Transfusion.*

Es werden je 1 Fall von Chloramin- und Anilinvergiftung beschrieben. Das Leben beider Kinder wurde augenscheinlich gerettet durch die Behandlung mit Austausch-Transfusion.

STEN AXTRUP: *Dos casos de envenenamiento tratados con ex-sanguino-transfusión.*

Se demuestra un caso de envenenamiento con cloramina, y otro con anilina, ambos en niños que, al parecer, se han salvado por medio de la ex-sanguinotransfusión.

Received 21.6. 1950.

The Children's Department,  
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## Interstitial Plasma Cell Pneumonia

### Report of 2 Cases

by

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During the last years pediatricians as well as pathologists have taken an increasing interest in interstitial plasma cell pneumonia. Particularly publications from Germany and Switzerland have attracted attention to the "new" disease among infants.

It is noteworthy that the disease has not till now been mentioned in either American, Spanish or Italian literature. The reason must be that the illness has not yet been observed in these countries.

In Scandinavia, LINELL in Sweden has reported 1 case and GORMSEN in Denmark has reported 2. From both Norway and Finland we lack information.

The first description of the illness is credited to the pathologist FEYERTER from Danzig in 1927. His report has been followed by many publications, especially from Germany and Switzerland (AMMICH, BENEKE, HUG, STIRNIMANN, BRIEGER and others).

### Case Records

*Case 1.* Boy (born Dec. 28, 1946, died March 27, 1947) born 8 weeks before term, birth weight 1650 g. When 10 days old he was brought to the pediatric department on account of prematurity and debility. He was the younger of two; a brother three years older was born at term and was healthy during infancy. He and his parents were in good health. His mother had gone through two abortions, two and one and one half years, resp., before the second delivery, and during both pregnancies she was healthy. The second delivery was slight and spontaneous and without complications to the infant, especially no attack of cyanosis or convulsions until admittance to the hospital. At home the infant was bottle fed, now and then with an oral catheter supplementary feeding because he would not suck well.

On examination we found an emaciated, drowsy, premature infant without focal symptoms of any illness. In hospital he received breast-milk, but owing to debility sucked badly. Only one week later he had made progress, though he had loose and somewhat frequent stools without mucus or blood intermingled.

Over a seven-week period he gained 450 g in weight, being nourished with human milk. The stools continued to be of the same character as mentioned above. He was not catarrhal and his temperature was normal.

After two months' stay in hospital he contracted a slight edema preputii, but it disappeared completely within three days and did not return until a few days before death. Gradually the infant put on flesh and gained weight satisfactorily. The stools remained unchanged in spite of several attempts at treatment. Twelve days before death occurred it was reported in his records that he took his bottle well, had gained and was getting along well with the exception of unaltered stools. During the following five days nothing remarkable happened. Seven days before death there was an attack of facial cyanosis accompanied by rapid, shallow respiration. The attack, however, disappeared spontaneously in a few minutes. Clinical examination revealed no pathologic findings over the lungs, heart or elsewhere. In the course of the following five hours there was passage of four loose stools. The abdomen was not distended or tender. Later on the infant whimpered for some hours. On the next morning a similar attack of tachypnea and cyanosis occurred and simultaneously a tachycardia was registered but further examination was without result. The attack again ceased rapidly but the infant continued during the day and the following night to be pale, restless and a little dyspneic without cough. His temperature was normal. The next morning he looked all right, and his heart beat in normal rhythm but his respiration was a little shallow. Two days later a slight attack occurred in the afternoon and a severe one in the evening in connection with feeding, with tremendously accelerated and superficial breathing accompanied by extreme cyanosis and rumbling of the bowels. After the cessation of the attack the infant recovered quickly. It was noteworthy that he took his bottle well between the attacks. The day before death another attack of the same character was seen but clinical examination revealed nothing but an uncertain impairment of the percussion and the auscultation — without rales — on the base of the left lung. The boy continued to be noncatarrhal and afebrile, but thereafter constant oxygen therapy was necessary. When drinking he had to make frequent interruptions, chiefly on account of increasing dyspnea. In the course of the day he was stimulated by repeated injections of sympatol and in addition he received a shock dose of sulfathiazole and penicillin every third hour as pneumonia was suspected. All day long the infant was in very bad condition though his temperature was steadily normal. In spite of the therapy mentioned above he died on the following day with symptoms similar to those of suffocation. The uncertain percussion and auscultatory changes over the left lung did not alter towards the end.

Sedimentation rate: 4 mm (a. m. Landau). Hgb 140, 83, 75, 78 %. Moro and Mantoux negative. Urine: no pathologic findings. Electro-

cardiogram was normal. In cultures (three) from the stools no pathogenic bacteria could be detected. Throat swabs revealed neither hemolytic streptococci nor pneumococci. The red and white blood counts showed normal values and there was no shift to the left in the hemogram. Roentgenogram of the chest (one and one half days before death): dim, confluent, ill defined, fairly extensive shadows in the center of both lungs, resembling pneumonia; no signs of pleurisy or atelectasis. The heart was of normal size and shape.

*Extract From the Postmortem Examination*

*(Courtesy of Dr. V. Friedenreich)*

There was slight edema of the buttocks and the preputium penis. The tongue, larynx, thyroid gland, thymus and trachea showed nothing remarkable. In both pleural cavities there was scarce, clear fluid and the surface was clean without hemorrhages. The lungs were large and heavy; in the tissue was found an extensive, almost completely diffuse pneumonic infiltration. The surface colour was relatively bright greyish-red with the exception of the right middle lobe, where the colour both on the surface and the cut surface was bright. Anterior in both upper lobes were bright areas in the tissue extensively infiltrated and differing from the surrounding pneumonic tissue by a more edematous appearance. From many areas of the infiltrated lung tissue a yellow fluid could be expressed. The lymph nodes of the hili were slightly enlarged, soft and somewhat red in colour. Along the trachea similar lymph nodes were found. On the front wall of the pericardium parietale a single small hemorrhage was present. Examination of the heart, aorta and vena cava sup. revealed nothing noteworthy. The spleen was somewhat enlarged, the surface remarkable bright, the cut surface bright, greyish-red, the consistency below normal. The esophagus, stomach, liver, gall bladder, colon, adrenal glands, kidneys and urinary bladder were all normal. The wall of the small bowels seemed to be a little edematous.

*Microscopic Examination of the Lungs etc.*

The microscopic picture of the lungs was homogeneous throughout. It was highly remarkable that the alveoli in all areas were filled with granular or slightly thready masses but showed a complete lack of inflammatory cells (Fig. 1). The covering of the alveolar walls was mostly well preserved and the alveoli were lined with cells, often of very large size and somewhat cuboidal or semicircular with large nucleoli. The interstitial spaces between the alveoli were to a great extent heavily thickened and contained numerous cells (which were partly lying inside the vessels). The cells were partly plasma cells but for the most part larger and smaller cells resembling the lymphocytes; practically no granulo-



Fig. 1. Case 1. The alveoli filled with a granular exudate containing remarkable few cells.

cytes were observed. There was moderate hyperemia. The bronchi contained in some places the same granular masses found in the alveoli; there were no signs of inflammation in the wall of the bronchi. The bronchial lymph nodes contained a small number of plasma cells. Liver: nothing noteworthy. Kidneys: in the capsule spaces granular masses of moderate degree. Small bowels: No signs of edema or inflammation. The other organs revealed no pathologic changes.

*Case 2.* A girl, twin born three weeks before term March 26, 1947, died July 4, 1947. She was admitted to the hospital 16 days old on account of prematurity, debility, bronchopneumonia and symptomatic dyspepsia. The other twin and the parents were healthy. The mother was primipara. The delivery was relatively easy and spontaneous, the infant weighing 2020 g and measuring 48 cm. She had been breast fed at home but had steadily lost weight chiefly because she had difficulty in sucking. On admission to the pediatric department of Sundby hospital we found a small, slender and emaciated infant weighing 1900 g and with symptoms of pneumonia of the left lung. She received a shock dose of sulfathiazole and recovered rapidly. But during all her stay in hospital



there remained a tendency to loose stools. At the beginning she received breast-milk and later on A-C-D-vitamins in addition. Nine days after admission a moderate edema on both legs developed but disappeared again in the course of the following six days. For the first two weeks she was debile but without symptoms of intracranial hemorrhage. By and by she sucked better and after a month had passed her weight had reached 2400 g, but still some difficulty in gaining persisted. After the pneumonia was cured the temperature remained normal but the stools continued to be loose and after two months' stay the development was still unsatisfactory. The girl was pale (hgb. 59 %) and received a blood transfusion and recovered a little. Eight days before death it was reported in her records that she was getting along better, looked well and was sucking better. But on the next morning the situation — in the course of a few minutes — suddenly altered completely. The infant became greyish-pale with rapid and shallow respiration accompanied by increasing cyanosis. In spite of negative lung findings on clinical examination she received, on suspicion of pneumonia, a shock dose of sulfathiazole and stimulated by several injections of sympatol during the next five hours recovered slowly. During the following night and the next morning she was still afebrile and noncatarrhal and sucked astonishingly well. On the third day after the first attack another one took place and again the following examination was negative (including examination of the spinal fluid). She was given, for safety's sake, penicillin every third hour. During the succeeding two days some degree of dyspnea was steadily present. She became cyanotic when bottlefed and the dyspnea increased simultaneously. From then on it was therefore necessary to give oxygen constantly. The day before death there was passage of two loose stools and a single vomiting. The last day of life a severe dyspnea accompanied by cyanosis was prevalent in spite of constant administration of oxygen. Over the lungs some rales were heard. She died in the night with symptoms similar to those in suffocation.

Sedimentation rate normal, hgb. 59—65 %. A persistent hypochromic anemia was present during the last month. Total white blood cell count 8800; differential cell count: polymorphonuclear 22 %, eosinophils 2 %, basophils 1 %, lymphocytes 75 %, plasma cells 0 %. Repeated blood examination revealed no real changes. The urine was normal and the Moro and Mantoux were negative. Wassermann reaction negative. Serum albumin and globulin examinations were not performed. Blood type 0, rhesus negative. The mother type 0, rhesus negative, serum did not contain antibodies. The father type 0, rhesus negative. X-ray of the lungs was not performed.

*Extract From the Postmortem Examination**(by Courtesy of Dr. V. Friedenreich)*

The lungs were solid and emptied of air, with a dark-reddish cut surface. The consistency was not brittle. There was no pus in the bronchioli. All the other organs show macroscopic normal circumstances.

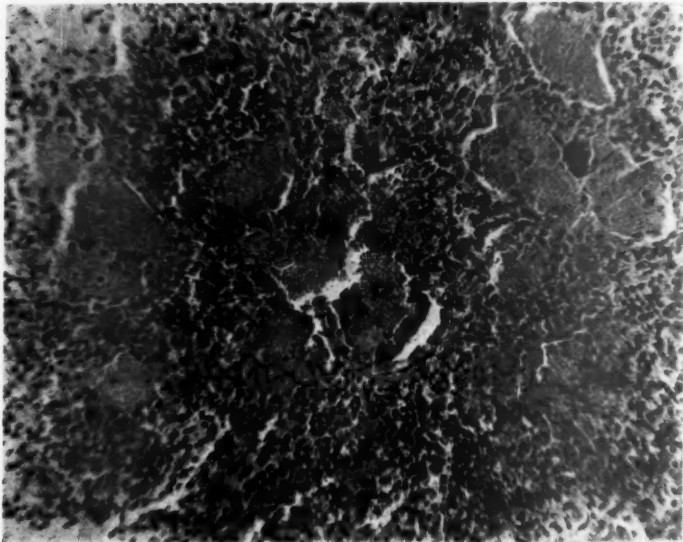


Fig. 2. Case 2. Enormous accumulation of plasma cells and cells resembling histiocytes in the interstitial spaces between the alveoli; remarkable lack of cells in the alveoli.

**Microscopic Examination of the Lungs.** The alveoli were filled with granular masses and, literally, there was a complete lack of inflammatory cells. The walls of the alveoli were in many areas covered with cloudy masses and in other parts of the lungs lined with hyperplastic peithelial cells. The interstitial spaces between the alveoli were enormously thickened and very rich in cells which were, practically without exception, mononuclear and to a large extent plasma. Further, bigger cells resembling the histiocytes and smaller ones like lymphocytes were seen. The bronchi contained in some areas granular masses as described

in the alveoli and in addition some desquamated cells. In the wall of the bronchi there was a slight infiltration of cells.

The diagnosis reported in both cases was: *Ante tempus natus, Debilitas congenita, Pneumonia fibrinosa and interstitialis* (the diagnosis last mentioned chiefly based upon the histologic findings).

Renewed examination of both the clinical course of the cases and the microscopic slides of the lungs established beyond doubt that the 2 cases described above were so-called interstitial plasma cell pneumonia.

Lastly I shall give a brief summary of the major features and symptoms common to both cases.

- 1) Birth before term.
- 2) A tendency to loose stools, long lasting and without containing pathogenic bacteria.
- 3) Transient edema.
- 4) Normal temperature and noncarrhal condition throughout the course of the disease.
- 5) Seven—eight days before death sudden and unexpected attacks of tachypnea accompanied by cyanosis. These returned at various intervals.
- 6) Both died with symptoms similar to those of suffocation.
- 7) Lack of focal symptoms until shortly before death, and then vague and non-characteristic findings in the lungs (in one case x-ray of the chest showed central changes in the lungs).
- 8) They died at about the same age, 13 and 14 weeks old, resp.

### Discussion

During the period 1935 to 1949 about 400 infants born before term have been admitted to the pediatric department of Sundby hospital, and among them 2 cases of interstitial plasma cell pneumonia have been diagnosed. I have further traced 875 cases of pneumonia which were hospitalized between Feb. 1, 1941, and Feb. 1, 1949, in the same department without finding any more cases. It is therefore not only probable but certain that the disease has hitherto been very rare in Copenhagen and, as mentioned at the beginning of this report, in Scandinavia as a whole up to present time.

The 2 cases reported occurred in close succession (March—July 1947).

The illness is presumed to be a disease of the first year of life only, as no case has hitherto been observed among infants older than 1 year. Usually the illness is encountered in the course of the first 6 months of life. With the exception of 2 cases, the disease has thus far not been observed in infants younger than 6 weeks. Most frequently it is seen

between the ninth and the eleventh weeks of life. The reports concerning the illness originate partly from postmortem examinations (FEYERTER and others) and partly from pediatric clinics where many cases have accumulated and appeared in waves. The author's 2 cases were both prematures and if we go over the literature we find that about 80—90 % of all plasma cell pneumonias occur among infants born before term. Further, the disease starts when the infant has overcome the difficulties of the first weeks of life and commences to gain weight. Single cases among infants with a birth weight between 2510 and 3000 g have been reported (TOBLER, STIRNIMANN, LINELL). HUG has stated a higher frequency among girls, but reviewing the present literature we find the cases about evenly distributed between the sexes.

The nature of the disease is still obscure. Many theories about the etiology have been put forth. At the present time an infectious origin is generally accepted. As to the symptomatology, some authors have pointed out that infections of the upper respiratory tracts may start the illness, but others deny this assumption. I have mentioned the tendency to loose stools and edemas during the earlier stages of the illness.

TOBLER calls attention to edemas at the height of the disease. The clinical course is characterized by lack of capital symptoms until the attacks of tachypnea accompanied by cyanosis (or steadily increasing dyspnea with various degree of cyanosis) commence, and even at that time it is often impossible to make an exact diagnosis. A roentgenogram of the lungs may or may not support the diagnosis. It is also obvious that the morbidity and death rate will differ greatly in different reports, as an exact diagnosis cannot yet be established with absolute certainty unless histologic examinations are performed. Till now symptomatic treatment of various kinds has been employed, but with doubtful effect. A causal therapy does not exist at the present time; perhaps the new antibiotics may be of some value.

### Summary

Report of 2 cases of interstitial plasma cell pneumonia.

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Received 26.6. 1950.

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